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(54) Title: THIOPHENE DERIVATIVES ACTIVE AS KINASE INHIBITORS, PROCESS FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS COMPRISING THEM

(57) Abstract: Compounds which are 3-aminocarbonyl-2-carboxamido-thiophene derivatives or pharmaceutically acceptable salts thereof, together with pharmaceutical compositions comprising them are disclosed; these compounds or compositions are useful in the treatment of diseases caused by and/or associated with an altered protein kinase activity such as cancer, cell proliferative disorders, Alzheimer's disease, viral infections, auto-immune diseases and neurodegenerative disorders.

THIOPHENE DERIVATIVES ACTIVE AS KINASE INHIBITORS, PROCESS FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS COMPRISING THEM

The present invention relates to thiophene derivatives active as kinase inhibitors and, more in particular, it relates to 3-aminocarbonyl-2-carboxamido-thiophene derivatives, to a process for their preparation, to pharmaceutical compositions comprising them and to their use as therapeutic agents, particularly in the treatment of diseases linked to disregulated protein kinases.

The malfunctioning of protein kinases (PKs) is the hallmark of numerous diseases. A large share of the oncogenes and proto-oncogenes involved in human cancers code for PKs. The enhanced activities of PKs are also implicated in many non-malignant diseases, such as benign prostate hyperplasia, familial adenomatosis, polyposis, neuro-fibromatosis, psoriasis, vascular smooth cell proliferation associated with atherosclerosis, pulmonary fibrosis, arthritis glomerulonephritis and post-surgical stenosis and restenosis.

PKs are also implicated in inflammatory conditions and in the multiplication of viruses and parasites. PKs may also play a major role in the pathogenesis and development of neurodegenerative disorders.

For a general reference to PKs malfunctioning or disregulation see, for instance, *Current Opinion in Chemical Biology* 1999,*3*, 459 - 465.

It is an object of the invention to provide compounds which are useful in therapy as agents against a host of diseases

caused by and/or associated to a disregulated protein kinase activity.

It is another object to provide compounds which are endowed with multiple protein kinase inhibiting activity.

The present inventors have now discovered that some 3-aminocarbonyl-2-carboxamido-thiophene derivatives are endowed with multiple protein kinase inhibiting activity and are thus useful in therapy in the treatment of diseases associated with disregulated protein kinases.

More specifically, the 3-aminocarbonyl-2-carboxamido-thiophene derivatives of this invention are useful in the treatment of a variety of cancers including, but not limited to: carcinoma such as bladder, breast, colon, kidney, liver, lung, including small cell lung cancer, esophagus, gall-bladder, ovary, pancreas, stomach, cervix, thyroid, prostate, and skin, including squamous cell carcinoma; hematopoietic tumors of lymphoid lineage, including leukemia, acute lymphocitic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T-cell-lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, hairy cell lymphoma and Burkett's lymphoma; hematopoietic tumors of myeloid lineage, including acute and chronic myelogenous leukemias, myelodysplastic syndrome and promyelocytic leukemia; tumors of mesenchymal origin, including fibrosarcoma and rhabdomyosarcoma; tumors of the central and peripheral nervous system, including astrocytoma, neuroblastoma, glioma and schwannomas; other tumors, including melanoma, seminoma, teratocarcinoma, osteosarcoma, xeroderma pigmentosum, keratoacanthoma, thyroid follicular cancer and Kaposi's sarcoma.

Due to the key role of PKs in the regulation of cellular proliferation, these 3-aminocarbonyl-2-carboxamido-thiophenes are also useful in the treatment of a variety of cell proliferative disorders such as, for instance, benign prostate hyperplasia, familial adenomatosis, polyposis,

neuro-fibromatosis, psoriasis, vascular smooth cell proliferation associated with atherosclerosis, pulmonary fibrosis, arthritis glomerulonephritis and post-surgical stenosis and restenosis.

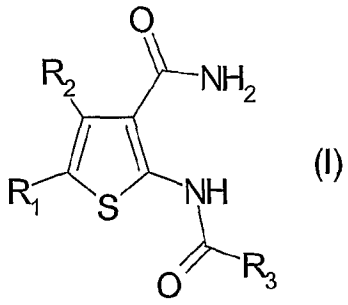
The compounds of the invention can be useful in the treatment of Alzheimer's disease, as suggested by the fact that cdk5 is involved in the phosphorylation of tau protein (*J. Biochem.*, 117, 741-749, 1995).

The compounds of this invention, as modulators of apoptosis, may also be useful in the treatment of cancer, viral infections, prevention of AIDS development in HIV-infected individuals, autoimmune diseases and neurodegenerative disorders.

The compounds of this invention may be useful in inhibiting tumor angiogenesis and metastasis.

The compounds of the invention are useful as cyclin dependent kinase (cdk) inhibitors and also as inhibitors of other protein kinases such as, for instance, protein kinase C in different isoforms, Met, PAK-4, PAK-5, ZC-1, STLK-2, DDR-2, Aurora 1, Aurora 2, Bub-1, PLK, Chk1, Chk2, HER2, raf1, MEK1, MAPK, EGF-R, PDGF-R, FGF-R, IGF-R, VEGF-R, PI3K, weel kinase, Src, Abl, Akt, ILK, MK-2, IKK-2, Cdc7, Nek, and thus be effective in the treatment of diseases associated with other protein kinases.

Accordingly, the present invention provides a method for treating diseases caused by and/or associated with an altered protein kinase activity, by administering to a mammal in need thereof an effective amount of a 3-aminocarbonyl-2-carboxamido-thiophene derivative represented by formula (I):



(I)

wherein

R_1 and R_2 are, independently from each other, hydrogen, halogen or an optionally substituted group selected from aryl, straight or branched C_1-C_6 alkyl or aryl C_1-C_6 alkyl or, taken together with the thiophene bond to which they are linked, R_1 and R_2 form a $-(CH_2)_m-(NR_4)_n-(CH_2)_p-$ group wherein m and p are, each independently, an integer from 1 to 3, n is 0 or 1 and m+n+p is an integer from 3 to 5; R_4 is hydrogen or an optionally substituted straight or branched C_1-C_6 alkyl group;

R_3 is a group, optionally further substituted, selected from:

i) straight or branched C_1-C_8 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl or C_2-C_6 alkylcarbonyl;

ii) aryl;

iii) 3 to 7 membered carbocycle;

iv) 5 to 7 membered heterocycle with from 1 to 3 heteroatoms selected among nitrogen, oxygen and sulfur;

or a pharmaceutically acceptable salt thereof.

In a preferred embodiment of the method described above, the disease caused by and/or associated with an altered protein kinase activity is selected from the group consisting of cancer, cell proliferative disorders, Alzheimer's disease, viral infections, auto-immune diseases and neurodegenerative disorders.

Specific types of cancer that may be treated include carcinoma, squamous cell carcinoma, hematopoietic tumors of myeloid or lymphoid lineage, tumors of mesenchymal origin, tumors of the central and peripheral nervous system, melanoma, seminoma, teratocarcinoma, osteosarcoma, xeroderma pigmentosum, keratoacanthoma, thyroid follicular cancer and Kaposi's sarcoma.

In another preferred embodiment of the method described above, the cell proliferative disorder is selected from the group consisting of benign prostate hyperplasia, familial adenomatosis polyposis, neuro-fibromatosis, psoriasis, vascular smooth cell proliferation associated with atherosclerosis, pulmonary fibrosis, arthritis glomerulonephritis and post-surgical stenosis and restenosis.

In addition, the method object of the present invention, also provides tumor angiogenesis and metastasis inhibition.

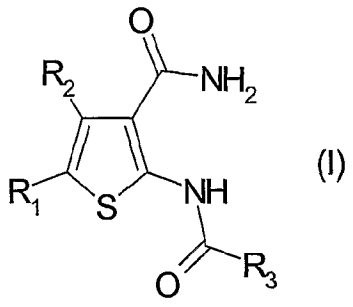
Several 3-aminocarbonyl-2-carboxamido-thiophene derivatives are known in the art, mostly as herbicides or synthetic intermediates and only few as therapeutic agents, particularly as anti-inflammatory agents.

See, for a general reference, Chemical Abstracts C.A. 108(1988):112332; 85(1976):123697; 112(1990):118758; DE-A-4039734 and FR-A-2035767.

The international patent application WO 98/54116 in the name of Cadus Pharmaceutical Co. discloses thiophene derivatives possessing antitumor activity.

The international patent application WO 00/71532 in the name of Pfizer Products Inc., discloses thiophene derivatives among which are ureido-thiophenes as anticancer agents.

The present invention thus provides a 3-aminocarbonyl-2-carboxamido-thiophene derivative represented by formula (I):



(I)

wherein

R_1 and R_2 are, independently from each other, hydrogen, halogen or an optionally substituted group selected from aryl, straight or branched C_1-C_6 alkyl or aryl C_1-C_6 alkyl or, taken together with the thiophene bond to which they are linked, R_1 and R_2 form a $-(CH_2)_m-(NR_4)_n-(CH_2)_p-$ group wherein m and p are, each independently, an integer from 1 to 3, n is 0 or 1 and m+n+p is an integer from 3 to 5; R_4 is hydrogen or an optionally substituted straight or branched C_1-C_6 alkyl group;

R_3 is a group, optionally further substituted, selected from:

i) straight or branched C_1-C_8 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl or C_2-C_6 alkylcarbonyl;

ii) aryl;

iii) 3 to 7 membered carbocycle;

iv) 5 to 7 membered heterocycle with from 1 to 3 heteroatoms selected among nitrogen, oxygen and sulfur;

or a pharmaceutically acceptable salt thereof.

The compounds of formula (I), object of the present invention may, have asymmetric carbon atoms and may therefore exist either as racemic admixtures or as individual optical isomers.

Accordingly, all the possible isomers and their admixtures and of both the metabolites and the pharmaceutically acceptable bio-precursors (otherwise referred to as pro-drugs) of the compounds of formula (I), as well as any therapeutic method of treatment comprising them, are also within the scope of the present invention.

As used herein, unless otherwise specified, with the term halogen atom we intend a chlorine, bromine, fluorine or iodine atom.

With the term straight or branched C_1-C_8 alkyl we intend a group such as, for instance, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, n-hexyl, n-heptyl, n-octyl and the like.

With the term straight or branched C_2-C_6 alkenyl group or C_2-C_6 alkynyl group we intend, for instance, vinyl, allyl, isopropenyl, 1-, 2- or 3-butenyl, isobutylenyl, ethynyl, 1- or 2-propynyl, butynyl and the like.

With the term 3 to 7 membered carbocycle we intend either a saturated or partially unsaturated cycloalkyl group such as, for instance, cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl or cycloheptyl as well as bridged cycloalkyl groups, e.g. norbornene.

With the term aryl, either as such or as arylalkyl group, we intend a mono-, bi- or poly- either carbocyclic as well as heterocyclic hydrocarbon with from 1 to 4 ring moieties, either fused or linked to each other by single bonds, wherein at least one of the carbocyclic or heterocyclic rings is aromatic.

Not limiting examples of aryl groups are, for instance, phenyl, indanyl, biphenyl, α- or β-naphthyl, fluorenyl, 9,10-dihydroanthracenyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolyl, imidazolyl, imidazopyridyl, 1,2-methylenedioxyphenyl, thiazolyl, isothiazolyl, pyrrolyl, pyrrolyl-phenyl, furyl, phenyl-furyl,

benzotetrahydrofuranyl, oxazolyl, isoxazolyl, pyrazolyl, chromenyl, thienyl, benzothienyl, isoindolinyl, benzoimidazolyl, tetrazolyl, tetrazolylphenyl, pyrrolidinyl-tetrazolyl, isoindolinyl-phenyl, quinolinyl, isoquinolinyl, 2,6-diphenyl-pyridyl, quinoxalinyl, pyrazinyl, phenyl-quinolinyl, benzofurazanyl, 1,2,3-triazolyl, 1-phenyl-1,2,3-triazolyl, and the like.

With the term 5 to 7 membered heterocycle, hence encompassing aromatic heterocycles also referred to as aryl groups, we further intend a saturated or partially unsaturated 5 to 7 membered carbocycle wherein one or more carbon atoms are replaced by heteroatoms such as nitrogen, oxygen and sulfur.

Examples of 5 to 7 membered heterocycles, optionally benzocondensed or further substituted, are 1,3-dioxolane, pyran, pyrrolidine, pyrroline, imidazolidine, pyrazolidine, pyrazoline, piperidine, piperazine, morpholine, tetrahydrofuran, azabicyclononane and the like.

According to the above meanings provided to the R_1, R_2 and R_3 substituents, any of the above groups may be further optionally substituted in any of the free positions by one or more groups, for instance 1 to 6 groups, selected from: halogen, nitro, oxo groups (=O), carboxy, cyano, alkyl, perfluorinated alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, amino groups and derivatives thereof such as, for instance, alkylamino, dialkylamino, arylamino, diarylamino, ureido, alkylureido or arylureido; carbonylamino groups and derivatives thereof such as, for instance, formylamino, alkylcarbonylamino, alkenylcarbonylamino, arylcarbonylamino, alkoxycarbonylamino; hydroxy groups and derivatives thereof such as, for instance, alkoxy, aryloxy, alkylcarbonyloxy, arylcarbonyloxy, cycloalkenyloxy or alkylideneaminooxy; carbonyl groups and derivatives thereof such as, for instance, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl,

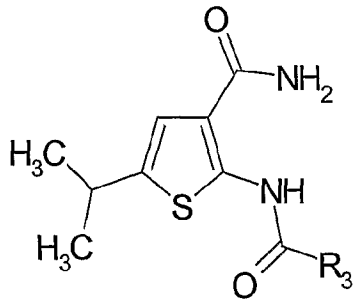
aryloxycarbonyl, cycloalkyloxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl; sulfurated derivatives such as, for instance, alkylthio, arylthio, alkylsulfonyl, arylsulfonyl, alkylsulfinyl, arylsulfinyl, arylsulfonyloxy, aminosulfonyl, alkylaminosulfonyl or dialkylaminosulfonyl. In their turn, whenever appropriate, each of the above substituents may be further substituted by one or more of the aforementioned groups.

Pharmaceutically acceptable salts of the compounds of formula (I) are the acid addition salts with inorganic or organic, e.g. nitric, hydrochloric, hydrobromic, sulfuric, perchloric, phosphoric, acetic, trifluoroacetic, propionic, glycolic, lactic, oxalic, malonic, malic, maleic, tartaric, citric, benzoic, cinnamic, mandelic, methanesulfonic, isethionic and salicylic acid, as well as the salts with inorganic or organic bases, e.g. alkali or alkaline-earth metals, especially sodium, potassium, calcium or magnesium hydroxides, carbonates or bicarbonates, acyclic or cyclic amines, preferably methylamine, ethylamine, diethylamine, triethylamine or piperidine.

Preferred compounds of the invention of formula (I) are the compounds wherein R_1 and R_2 are selected, each independently, from hydrogen, C_1-C_4 alkyl or optionally substituted aryl or aryl C_1-C_4 alkyl groups and R_3 has the above reported meanings.

Also preferred are the compounds of formula (I) wherein R_1 and R_2, together, form a $-(CH_2)_m-(NR_4)_n-(CH_2)_p-$ group, n is 0 or 1, R_4 if present is C_1-C_4 alkyl, preferably methyl, m+n+p is 4 and R_3 has the above reported meanings.

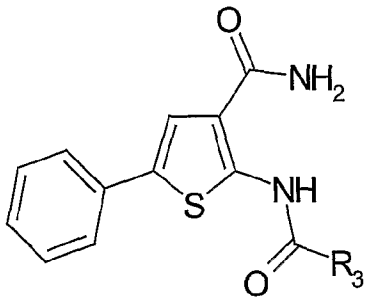
Within the aforementioned compounds of formula (I) particularly preferred are those wherein R_1 is isopropyl and R_2 is hydrogen, of formula (Ia) below



(Ia)

and wherein R_3 is as above defined.

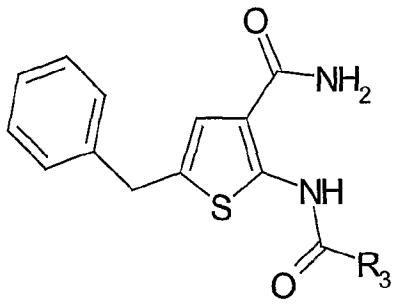
Another class of preferred compounds of formula (I) are those wherein R_1 is phenyl and R_2 is hydrogen, of formula (Ib) below



(Ib)

and wherein R_3 is as above defined; provided that R_3 is other than methyl, phenyl, 2-carboxyethyl, 2-thienyl, 2-furyl, pyrrolidin-1-yl-methyl or piperidyl-1-yl-methyl.

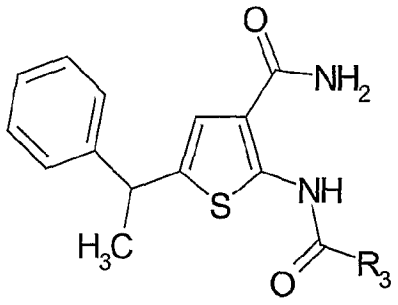
Another class of preferred compounds of formula (I) are those wherein R_1 is phenylmethyl and R_2 is hydrogen, of formula (Ic) below



(Ic)

and wherein R_3 is as above defined.

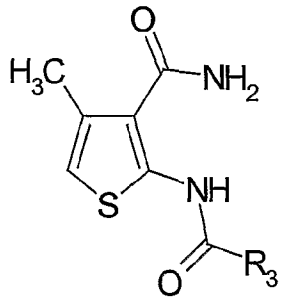
Another class of preferred compounds of formula (I) are those wherein R_1 is 1-phenyl-ethyl and R_2 is hydrogen, of formula (Id) below



(Id)

and wherein R_3 is as above defined.

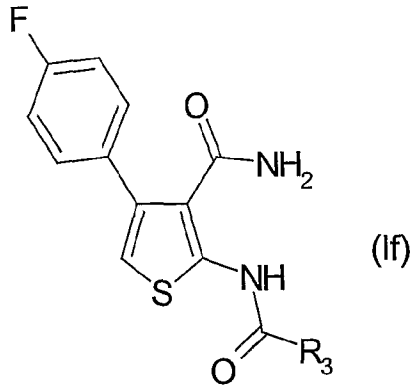
Another class of preferred compounds of formula (I) are those wherein R_1 is hydrogen and R_2 is methyl, of formula (Ie) below



(Ie)

and wherein R_3 is as above defined; provided that R_3 is other than n-propyl, n-butyl or optionally further substituted nitrophenyl.

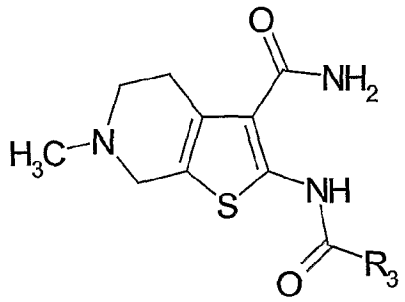
Another class of preferred compounds of formula (I) are those wherein R_1 is hydrogen and R_2 is 4-fluorophenyl, of formula (If) below



(If)

and wherein R_3 is as above defined.

Another class of preferred compounds of formula (I) are those wherein R_1 and R_2 together form a $-(CH_2)_m-(NR_4)_n-(CH_2)_p-$ group wherein m is 2, n and p are both 1, R_4 is methyl, of formula (Ig) below



(Ig)

and wherein R_3 is as above defined; provided that R_3 is other than ethoxycarbonyl, ethoxycarbonylmethyl or methylcarbonylmethyl.

The aforementioned compounds of formula (Ib) wherein R_3 is methyl or phenyl are disclosed as synthetic intermediates in J. Chem. Soc., Perkins Trans. 1 (1987), 7, 1457-63; the compound of formula (Ib) wherein R_3 is 2-carboxyethyl is reported in Chemical Abstracts C.A. 113(1990):40617, as synthetic intermediate; the compounds of formula (Ib) wherein R_3 is 2-thienyl, 2-furyl, pyrrolidin-1-yl-methyl or piperidyl-1-yl-methyl are all known as commercially available compounds.

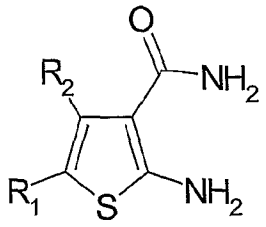
The aforementioned compounds of formula (Ie) wherein R_3 is n-propyl or n-butyl are disclosed in the international patent application WO 93/03040 by Taisho Pharmaceutical; the compounds of formula (Ie) wherein R_3 is an optionally further substituted nitrophenyl group are disclosed as synthetic intermediates in Chemical Abstracts C.A. 125(1996):168012.

The aforementioned compounds of formula (Ig) wherein R_3 is ethoxycarbonyl (-COOEt), ethoxycarbonylmethyl ($-CH_2$-COOEt) or methylcarbonylmethyl ($-CH_2$-CO-CH_3) are known as chemical intermediates, as reported in Chemical Abstracts C.A. 112(1990):216410.

All of the preferred compounds of the invention, whenever appropriate in the form of pharmaceutically acceptable salts, e.g. hydrobromide or hydrochloride salts, are herewith conveniently indicated and defined as products by process, that is as products of formula (I) which are obtainable, for instance through a defined a process.
More in particular, specific preferred compounds (I) of the invention are the compounds which are obtainable, for instance through a combinatorial chemistry technique, by reacting each of the amino-thiophene derivatives of formula (II), as set forth in table I, with any one of the carboxylic acid derivatives of formula R_3-COOH (III), as set forth in table II.

Table I

Amino-thiophene derivatives of formula (II)



(II)

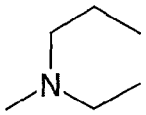
R_1	R_2
Isopropyl	Hydrogen
Phenyl	Hydrogen
Phenylmethyl	Hydrogen
1-phenylethyl	Hydrogen
Methyl	Methyl
Hydrogen	Methyl
Hydrogen	4-fluorophenyl
$-(CH_2)_4-$	
$-CH_2-N(CH_3)-(CH_2)_2-$ 	

Table II

Carboxylic acid derivatives of formula R_3-COOH (III)

Entry	R_3-COOH	Entry	R_3-COOH
1.	ACETIC	5.	CYCLOPROPANECARBOXYLIC
2.	PROPIONIC	6.	ISOBUTYRIC
3.	2-BUTYNOIC	7.	3,3-DIMETHYLACRYLIC
4.	CYANOACETIC	8.	2-KETOBUTYRIC

Table II cont.

9.	N,N-DIMETHYLGLYCINE	45.	UROCANIC
10.	3-CHLOROPROPIONIC	46.	2-METHYLPYRAZINE-5-CARBOXYLIC
11.	PYRROLE-2-CARBOXYLIC	47.	5-NORBORNENE-2-CARBOXYLIC
12.	1-CYANOCYCLOPROPANECARBOXYLIC	48.	2-FLUOROBENZOIC
13.	PYRROLE-3-CARBOXYLIC	49.	3-FLUOROBENZOIC
14.	4-PYRAZOLECARBOXYLIC	50.	4-FLUOROBENZOIC

15.	IMIDAZOL-4-CARBOXYLIC	51.	3,5-DIMETHYLISOXAZOLE-4-CARBOXYLIC
16.	CYCLOPENTANECARBOXYLIC	52.	THIOPHENE-2-ACETIC
17.	N-ACETYLGLYCINE	53.	THIOPHENE-3-ACETIC
18.	BENZOIC	54.	3-CYCLOPENTYLPROPIONIC
19.	PICOLINIC	55.	CYCLOHEPTANECARBOXYLIC
20.	NICOTINIC	56.	2,2-DIMETHYLHEXANOIC
21.	ISONICOTINIC	57.	ALPHA-(ISOPROPYLIDENEAMINOOXY)PROPIONIC
22.	2-PYRAZINECARBOXYLIC	58.	N,N-DIMETHYLSUCCINAMIC
23.	1-METHYLPYRROLE-2-CARBOXYLIC	59.	PHENYLPROPIOLIC
24.	3-METHYL-2-FUROIC	60.	N-CARBAMYL-DL-ALPHA-AMINO-N-BUTYRIC
25.	5-METHYLISOXAZOLE-4-CARBOXYLIC	61.	3-CYANOBENZOIC
26.	3-METHYLISOXAZOLE-4-CARBOXYLIC	62.	4-CYANOBENZOIC
27.	5-METHYLISOXAZOLE-3-CARBOXYLIC	63.	N-METHYL-L-PROLINE MONOHYDRATE
28.	3-AMINOPYRAZOLE-4-CARBOXYLIC	64.	TRANS-CINNAMIC
29.	THIOPHENE-2-CARBOXYLIC	65.	3-(3-PYRIDYL)ACRYLIC
30.	THIOPHENE-3-CARBOXYLIC	66.	3-(4-PYRIDYL)-ACRYLIC
31.	CYCLOPENTYLACETIC	67.	2,3-DIMETHYLBENZOIC
32.	DL-PYROGLUTAMIC	68.	2,4-DIMETHYLBENZOIC
33.	1-(AMINOCARBONYL)-1-CYCLOPROPANECARBOXYLIC	69.	2,5-DIMETHYLBENZOIC
34.	N-ME-PRO-OH	70.	2,6-DIMETHYLBENZOIC
35.	2-IMIDAZOLIDONE-4-CARBOXYLIC	71.	3,4-DIMETHYLBENZOIC
36.	N-ACETYL-DL-ALANINE	72.	3,5-DIMETHYLBENZOIC
37.	3-UREIDOPROPIONIC	73.	2-PHENYLPROPIONIC
38.	O-TOLUIC	74.	HYDROCINNAMIC
39.	M-TOLUIC	75.	O-TOLYLACETIC
40.	P-TOLUIC	76.	M-TOLYLACETIC
41.	PHENYLACETIC	77.	P-TOLYLACETIC
42.	SALICYLIC	78.	3-PYRIDINEPROPIONIC
43.	3-HYDROXYBENZOIC	79.	O-ANISIC
44.	4-HYDROXYBENZOIC	80.	3-METHYLSALICYLIC

Table II cont.

81.	4-METHYLSALICYLIC	117.	INDOLE-5-CARBOXYLIC
82.	5-METHYLSALICYLIC	118.	INDOLE-4-CARBOXYLIC
83.	3-METHOXYBENZOIC	119.	INDOLE-6-CARBOXYLIC
84.	3-HYDROXY-4-METHYLBENZOIC	120.	BENZOFURAN-2-CARBOXYLIC

85.	P-ANISIC	121.	5-BENZIMIDAZOLECARBOXYLIC
86.	PHENOXYACETIC	122.	INDAZOLE-3-CARBOXYLIC
87.	2-HYDROXYPHENYLACETIC	123.	1-PHENYL-1-CYCLOPROPANECARBOXYLIC
88.	3-HYDROXYPHENYLACETIC	124.	ALPHA-METHYLCINNAMIC
89.	4-HYDROXYPHENYLACETIC	125.	4-IMIDAZOLEACETIC HYDROCHLORIDE
90.	DL-MANDELIC	126.	6-CARBOXYPURINE
91.	3-HYDROXY-O-TOLUIC	127.	2-ACETYLBENZOIC
92.	ALPHA-FLUOROPHENYLACETIC	128.	4-ACETYLBENZOIC
93.	2-FLUOROPHENYLACETIC	129.	O-COUMARIC
94.	3-FLUOROPHENYLACETIC	130.	3-HYDROXYCINNAMIC
95.	4-FLUOROPHENYLACETIC	131.	4-HYDROXYCINNAMIC
96.	3-(2-THIENYL)ACRYLIC	132.	P-COUMARIC
97.	3-(3-THIENYL)-ACRYLIC	133.	4-ISOPROPYLBENZOIC
98.	3-(2-THIENYL)PROPANOIC	134.	2-(3,5-XYLYL)ACETIC
99.	CYCLOHEPTYLACETIC	135.	PHTHALAMIC
100.	2-CHLOROBENZOIC	136.	3-DIMETHYLAMINOBENZOIC
101.	3-CHLOROBENZOIC	137.	4-DIMETHYLAMINOBENZOIC
102.	4-CHLOROBENZOIC	138.	2-DIMETHYLAMINOBENZOIC
103.	N-PROPYLMALEAMIC	139.	PIPERONYLIC
104.	N-ACETYL-DL-ALLYLGLYCINE	140.	ALPHA-FLUOROCINNAMIC
105.	AC-DL-PRO-OH	141.	3-METHOXY-4-METHYLBENZOIC
106.	1-PIPERIDINEPROPIONIC	142.	4-HYDROXY-3,5-DIMETHYLBENZOIC
107.	2-CHLORONICOTINIC	143.	BENZYLOXYACETIC
108.	6-CHLORONICOTINIC	144.	4-DIMETHYLAMINOBUTYRIC HYDROCHLORIDE
109.	N-CARBAMOYLMALEAMIC	145.	3-METHOXYSALICYLIC
110.	N-(ACETOACETYL)GLYCINE	146.	4-METHOXYSALICYLIC
111.	N-ACETYL-DL-VALINE	147.	5-METHOXYSALICYLIC
112.	N-CARBAMYL-DL-NORVALINE	148.	3-HYDROXY-4-METHOXYBENZOIC
113.	N-CARBAMYL-DL-VALINE	149.	VANILLIC
114.	DL-ALANYL-DL-ALANINE	150.	4-HYDROXYPHENOXYACETIC
115.	INDOLE-2-CARBOXYLIC	151.	6-METHOXYSALICYLIC
116.	INDOLE-3-CARBOXYLIC	152.	N-(2-FUROYL)GLYCINE

Table II cont.

153.	BETA-MALEIMIDOPROPIONIC	188.	ARECAIDINE HYDROCHLORIDE
154.	3,4-DIHYDRO-2,2-DIMETHYL-4-OXO-2H-PYRAN-6-CARBOXYLIC	189.	3-BENZOYLPROPIONIC
155.	5-ACETYLTHIOPHENE-2-CARBOXYLIC	190.	4-METHOXYCINNAMIC
156.	1-ACETYLPIPERIDINE-4-CARBOXYLIC	191.	2-METHOXYCINNAMIC

157.	1-NAPHTHOIC	192.	BENZO[B]THIOPHENE-2-CARBOXYLIC
158.	2-NAPHTHOIC	193.	2-ISOPROPYL-2-PHENYLACETIC
159.	4-CHLOROSALICYLIC	194.	N-ACETYLANTHRANILIC
160.	5-CHLOROSALICYLIC	195.	4-ACETAMIDOBENZOIC
161.	3-CHLORO-4-HYDROXYBENZOIC	196.	HIPPURIC
162.	3-CHLOROSALICYLIC	197.	3-ACETAMIDOBENZOIC
163.	AC-HYP-OH	198.	N-CHLOROACETYL-DL-2-AMINO-N-BUTYRIC
164.	QUINALDIC	199.	3,4-METHYLENEDIOXYPHENYLACETIC
165.	QUINOLINE-3-CARBOXYLIC	200.	NICOTINURIC
166.	QUINOLINE-4-CARBOXYLIC	201.	4-ISOPROPOXYBENZOIC
167.	1-ISOQUINOLINECARBOXYLIC	202.	3-(DIETHYLAMINO)PROPIONIC HYDROCHLORIDE
168.	QUINOLINE-6-CARBOXYLIC	203.	2,5-DIMETHOXYBENZOIC
169.	QUINOLINE-8-CARBOXYLIC	204.	2,6-DIMETHOXYBENZOIC
170.	6-ACETAMIDOHEXANOIC	205.	3,4-DIMETHOXYBENZOIC
171.	N-ACETYL-DL-LEUCINE	206.	3,5-DIMETHOXYBENZOIC
172.	N,N-DI-N-PROPYL-L-ALANINE	207.	2-METHOXYPHENOXYACETIC
173.	NALPHA-ACETYL-L-ASPARAGINE	208.	THYMINE-1-ACETIC
174.	CINNOLINE-4-CARBOXYLIC	209.	3-(2-THENOYL)-PROPIONIC
175.	2-QUINOXALINECARBOXYLIC	210.	3-CHLORO-4-METHOXYBENZOIC
176.	3-METHYLINDENE-2-CARBOXYLIC	211.	5-CHLORO-2-METHOXYBENZOIC
177.	INDOLE-3-ACETIC	212.	1-(2-CARBOXYPHENYL)PYRROLE
178.	1-METHYLINDOLE-2-CARBOXYLIC	213.	4-(1 H-PYRROL-1-YL)BENZOIC
179.	5-METHYLINDOLE-2-CARBOXYLIC	214.	3-INDOLEPROPIONIC
180.	1-METHYLINDOLE-3-CARBOXYLIC	215.	2-METHYL-3-INDOLEACETIC
181.	INDAZOLONE-4-CARBOXYLIC	216.	1-METHYL-3-INDOLEACETIC
182.	3-OXO-1-INDANCARBOXYLIC	217.	2-(TRIFLUOROMETHYL)BENZOIC
183.	2-METHYL-1H-BENZIMIDAZOLE-5-CARBOXYLIC	218.	3-(TRIFLUOROMETHYL)BENZOIC
184.	1,2,3,4-TETRAHYDRO-2-NAPHTHOIC	219.	4-(TRIFLUOROMETHYL)BENZOIC
185.	2-INDANYLACETIC	220.	CHROMONE-2-CARBOXYLIC
186.	1-METHYL-4-IMIDAZOLE-ACETIC HYDROCHLORIDE	221.	CHROMONE-3-CARBOXYLIC
187.	5-HYDROXYINDOLE-2-CARBOXYLIC	222.	3-HYDROXY-2-QUINOXALINECARBOXYLIC

Table II cont.

223.	2-BENZIMIDAZOLEPROPIONIC	258.	5-METHYL-3-PHENYLISOXAZOLE-4-CARBOXYLIC
224.	1-PHENYL-1-CYCLOPENTANECARBOXYLIC	259.	2-HYDROXY-5-(1 H-PYRROL-1-YL)BENZOIC
225.	2,3-DICHLOROBENZOIC	260.	4-METHYL-2-PHENYL-1,2,3-TRIAZOLE-5-CARBOXYLIC
226.	2,4-DICHLOROBENZOIC	261.	INDOLE-3-BUTYRIC

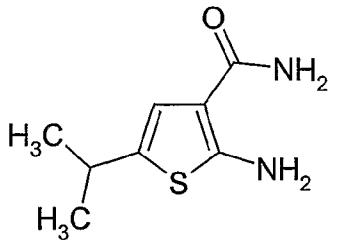
227.	2,5-DICHLOROBENZOIC	262.	AC-DL-PHE-OH
228.	2,6-DICHLOROBENZOIC	263.	2,3-DIMETHOXYCINNAMIC
229.	3,4-DICHLOROBENZOIC	264.	2,5-DIMETHOXYCINNAMIC
230.	3,5-DICHLOROBENZOIC	265.	3,4-DIMETHOXYCINNAMIC
231.	5-METHOXYINDOLE-2-CARBOXYLIC	266.	3,5-DIMETHOXYCINNAMIC
232.	5-HYDROXYINDOLE-3-ACETIC	267.	2,4-DIMETHOXYCINNAMIC
233.	4-OXO-4-PHENYLAMINO-2-BUTENOIC	268.	4-CHLOROINDOLE-3-ACETIC
234.	4-(DIMETHYLAMINO)CINNAMIC	269.	3-(3,4-DIMETHOXYPHENYL)PROPIONIC
235.	3,4-METHYLENEDIOXYCINNAMIC	270.	9-FLUORENECARBOXYLIC
236.	7-METHOXYBENZOFURAN-2-CARBOXYLIC	271.	6-CHLORO(2H)-1-BENZOPYRAN-3-CARBOXYLIC
237.	4-BENZOYLBUTYRIC	272.	EPSILON-MALEIMIDOCAPROIC
238.	BENZO[B]THIOPHENE-3-ACETIC	273.	2,3,4-TRIMETHOXYBENZOIC
239.	5-FLUOROINDOLE-3-ACETIC	274.	2,4,5-TRIMETHOXYBENZOIC
240.	N-BENZOYL-BETA-ALANINE	275.	3,4,5-TRIMETHOXYBENZOIC
241.	AC-DL-PHG-OH	276.	2,4,6-TRIMETHOXYBENZOIC
242.	BZ-ALA-OH	277.	3-CHLOROBENZO[B]THIOPHENE-2-CARBOXYLIC
243.	N-METHYLHIPPURIC	278.	3-(PHENYLSULFONYL)PROPIONIC
244.	O-HYDROXYHIPPURIC	279.	4-TOLUENESULFONYLACETIC
245.	FA-GLY-OH	280.	4-METHYLSULFONYLPHENYLACETIC
246.	5-CHLOROINDOLE-2-CARBOXYLIC	281.	D-DESTHIOBIOTIN
247.	(3,5-DIMETHOXYPHENYL)ACETIC	282.	3-PHTHALIMIDO-PROPIONIC
248.	3,5-DIMETHOXY-4-METHYLBENZOIC	283.	5-METHOXY-2-METHYL-3-INDOLEACETIC
249.	(2,4-DIMETHOXY-PHENYL)-ACETIC	284.	5-METHOXY-1-INDANONE-3-ACETIC
250.	N-ACETYL-L-HISTIDINE	285.	5-(4-CHLOROPHENYL)-2-FUROIC
251.	5-(2-THIENOYL)BUTYRIC	286.	6-CHLOROKYNURENIC
252.	4-(METHYLSULFONYL)BENZOIC	287.	N-(4-CHLOROPHENYL)MALEAMIC
253.	PHENYLSULFONYLACETIC	288.	N-P-TOSYLGLYCINE
254.	3-(METHYLSULFONYL)BENZOIC	289.	4,6-DICHLOROINDOLE-2-CARBOXYLIC
255.	2-(METHYLSULFONYL)BENZOIC	290.	N-(1-NAPHTHYL)MALEAMIC
256.	4-CARBOXYBENZENESULFONAMIDE	291.	3-IODOBENZOIC
257.	5-METHYL-1-PHENYLPYRAZOLE-4-CARBOXYLIC	292.	4-IODOBENZOIC

Table II cont.

293.	N-M-TOLYLPHTHALAMIC	298.	4-IODOPHENYLACETIC
294.	3-ACETAMINO-6-BROMOBENZOIC	299.	8-(3-CARBOXYPROPYL)-1,3-DIMETHYLXANTHINE

295.	2-ACETAMIDO-5-BROMOBENZOIC	300.	7-BROMOKYNURENIC
296.	BZ-HIS-OH	301.	N-BENZOYL-DL-PHENYLALANINE
297.	2-IODOPHENYLACETIC	--	

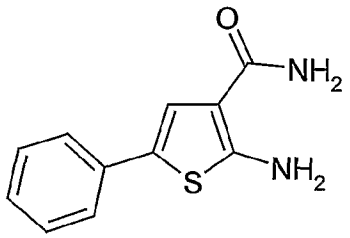
More specifically, herewith provided are novel compounds of formula (I) which are obtainable through a process comprising reacting the 2-amino-thiophene derivative of formula (II)



(II)

with each one of the carboxylic acids listed in table II.

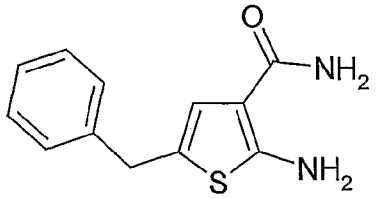
Also provided are novel compounds of formula (I) which are obtainable through a process comprising reacting the 2-amino-thiophene derivative of formula (II)



(II)

with each one of the carboxylic acids listed in table II other than acetic, benzoic or thiophene-2-carboxylic acid.

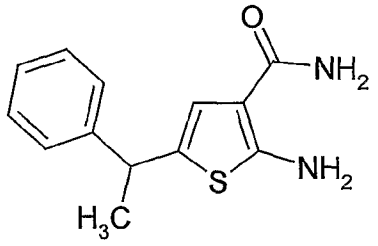
Also provided are novel compounds of formula (I) which are obtainable through a process comprising reacting the 2-amino-thiophene derivative of formula (II)



(II)

with each one of the carboxylic acids of table II.

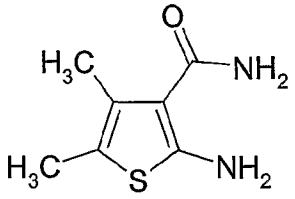
Also provided are novel compounds of formula (I) which are obtainable through a process comprising reacting the 2-amino-thiophene derivative of formula (II)



(II)

with each one of the carboxylic acids of table II.

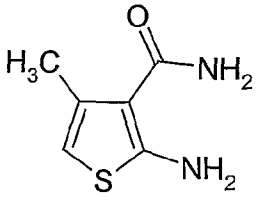
Also provided are novel compounds of formula (I) which are obtainable through a process comprising reacting the 2-amino-thiophene derivative of formula (II)



(II)

with each one of the carboxylic acids of table II.

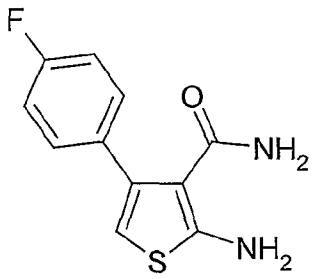
Also provided are novel compounds of formula (I) which are obtainable through a process comprising reacting the 2-amino-thiophene derivative of formula (II)



(II)

with each one of the carboxylic acids of table II.

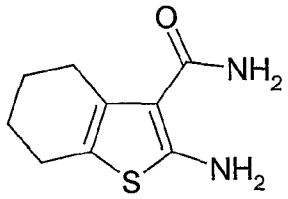
Also provided are novel compounds of formula (I) which are obtainable through a process comprising reacting the 2-amino-thiophene derivative of formula (II)



(II)

with each one of the carboxylic acids of table II.

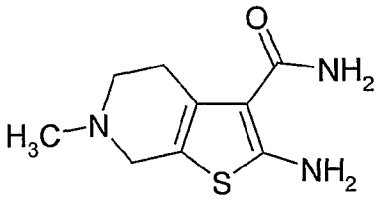
Also provided are novel compounds of formula (I) which are obtainable through a process comprising reacting the 2-amino-thiophene derivative of formula (II)



(II)

with each one of the carboxylic acids of table II.

Also provided are novel compounds of formula (I) which are obtainable through a process comprising reacting the 2-amino-thiophene derivative of formula (II)

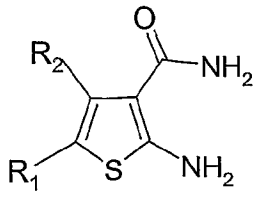


(II)

with each one of the carboxylic acids of table II.

As set forth above, it is a further object of the present invention a process for preparing the 3-aminocarbonyl-2-carboxamido-thiophene derivatives of formula (I).

The compounds of formula (I) and the salts thereof may be obtained, for instance, by a process comprising reacting a compound of formula (II)



(II)

with a compound of formula (III)

(III)

wherein R_1, R_2 and R_3 are as defined above and X is hydroxy or a suitable leaving group; and, if desired, converting a 2-aminocarbonyl-3-carboxamido-thiophene derivative of formula (I) into another such derivative of formula (I), and/or into a salt thereof.

Examples of specific leaving groups X within the compounds of formula (III) are halogen atoms.
Preferably, X is hydroxy, chlorine or bromine.
It is clear to the person skilled in the art that if a compound of formula (I), prepared according to the above process, is obtained as an admixture of isomers, their separation into the single isomers of formula (I) carried out according to conventional techniques, is still within the scope of the present invention.
Likewise, the conversion into the free compound (I) of a corresponding salt thereof, according to well-known procedures in the art, is still within the scope of the invention.
The above process is an analogy process which can be carried out according to well known methods.

The reaction between a compound of formula (II) and a carboxylic of formula (III) wherein X is hydroxy can be carried out in the presence of a coupling agent such as,

for instance, carbodiimide, i.e. 1,3-dicyclohexylcarbodiimide, 1,3-diisopropylcarbodiimide, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, N-cyclohexylcarbodiimide-N'-propyloxymethyl polystyrene or N-cyclohexylcarbodiimide-N'-methyl polystyrene, in a suitable solvent such as, for instance, dichloromethane, chloroform, tetrahydrofuran, diethyl ether, 1,4-dioxane, acetonitrile, toluene, or N,N-dimethylformamide at a temperature ranging from about -10°C to reflux for a suitable time, i.e. from about 30 min. to about 96 hours. The said reaction is optionally carried out in the presence of a suitable catalyst, for instance 4-dimethylaminopyridine, or in the presence of a further coupling reagent such as N-hydroxybenzotriazole.

The reaction between a compound of formula (II) and a compound of formula (III) can be also carried out, for example, through a mixed anhydride method, by using an alkyl chloroformate, such as ethyl, iso-butyl, or iso-propyl chloroformate, in the presence of a tertiary base, such as triethylamine, N,N-diisopropylethylamine or pyridine, in a suitable solvent such as, for instance, toluene, dichloromethane, chloroform, tetrahydrofuran, acetonitrile, diethyl ether, 1,4-dioxane, or N,N-dimethylformamide, at a temperature ranging from about -30°C to room temperature.

The reaction between a compound of formula (II) and a carboxylic derivative of formula (III) wherein X is a suitable leaving group can be carried out in the presence of a tertiary base, such as triethylamine, N,N-diisopropylethylamine or pyridine, in a suitable solvent, such as toluene, dichloromethane, chloroform, diethyl ether, tetrahydrofuran, acetonitrile, or N,N-dimethylformamide, at a temperature ranging from about -10°C to reflux.

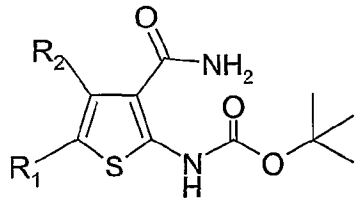
Also the optional conversion of a compound of formula (I) into another compound of formula (I) can be carried out according to known methods.

As an example, an alkylthio or an arylthio group may be converted into the corresponding alkylsulfonyl and arylsulfonyl group by reaction, for example, with m-chloroperbenzoic in a suitable solvent such as dichloromethane or chloroform, at a temperature varying between about -5°C and room temperature.

The optional salification of a compound of formula (I) or the conversion of its salt into the free compound, as well as the separation of a mixture of isomers into the single isomers, may all be carried out by conventional methods.

The compounds of formula (II) and (III) according to the process object of the present invention are known compounds or can be obtained according to known methods.

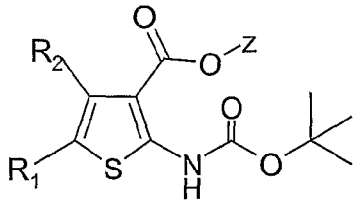
For example, a compound of formula (II) wherein R_1 and R_2 are as defined above can be obtained from a compound of formula (IV)



(IV)

by treatment with an organic or mineral acid, for instance trifluoroacetic or hydrochloric acid, in a suitable solvent such as tetrahydrofuran, dichloromethane, at a temperature varying between -10°C and reflux, for a time ranging from about 1 hour to about 24 hours.

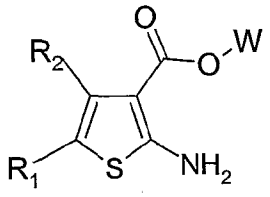
A compound of formula (IV), in its turn, can be obtained by treating the corresponding carboxylic derivative of formula (V), wherein R_1 and R_2 are as defined above and Z is chlorine, methoxy, or ethoxy



(V)

with ammonia in a suitable solvent such as dioxane, dichloromethane or acetonitrile. Also the optional conversion of a compound of formula (V) into another compound of formula (V) can be carried out according to known methods.

A compound of formula (V) can be obtained by treating the corresponding amino derivative (VI), wherein R_1 and R_2 are as defined above and W is methoxy, or ethoxy



(VI)

with di-t-butyl-dicarbonate in a suitable solvent such as dioxane, dichloromethane or acetonitrile, in the presence of a proton scavenger such as triethylamine or diisopropylethylamine at a temperature ranging from 0°C to reflux.

Compounds of formula (VI) are either commercially available compounds or can be prepared from commercially available precursors according to known methodologies, for instance as described in Chem. Ber. 1966, 99, 94; and J. Med. Chem. 1981, 24, 878.

A compound of formula (III) wherein X is a leaving group as defined above can be obtained according to conventional techniques from the corresponding carboxylic acids of formula (III) wherein X is hydroxy.

When preparing the compounds of formula (I) according to the process object of the present invention, optional functional groups within both the starting materials or the intermediates thereof, which could give rise to unwanted

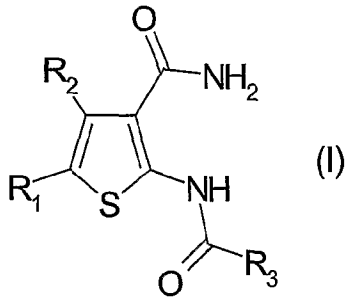
side reactions, need to be properly protected according to conventional techniques.

Likewise, the conversion of these latter into the free deprotected compounds may be carried out according to known procedures.

The compounds of formula (I) of the invention were prepared according to combinatorial chemistry techniques widely known in the art, by accomplishing the aforementioned condensation reactions between the compounds of formula (II) with those of formula (III) in a serial manner.

As an example, the compounds of the invention may be prepared by reacting each of the amino derivatives of formula (II) wherein R_1 and R_2 are as above defined, for instance as reported in table I, with each of the carboxylic acids of formula (III), as per table II, wherein R_3 is as above defined, or derivatives thereof wherein X is a suitable leaving group.

Accordingly, it is a further object of the present invention a library of two or more 3-aminocarbonyl-2-carboxamido-thiophene derivatives of formula (I)



(I)

wherein

R_1 and R_2 are, independently from each other, hydrogen, halogen or an optionally substituted group selected from aryl, straight or branched C_1-C_6 alkyl or aryl C_1-C_6 alkyl or, taken together with the thiophene bond to which they

are linked, R_1 and R_2 form a $-(CH_2)_m-(NR_4)_n-(CH_2)_p-$ group wherein m and p are, each independently, an integer from 1 to 3, n is 0 or 1 and m+n+p is an integer from 3 to 5; R_4 is hydrogen or an optionally substituted straight or branched C_1-C_6 alkyl group;

R_3 is a group, optionally further substituted, selected from:

i) straight or branched C_1-C_8 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl or C_2-C_6 alkylcarbonyl;

ii) aryl;

iii) 3 to 7 membered carbocycle;

iv) 5 to 7 membered heterocycle with from 1 to 3 heteroatoms selected among nitrogen, oxygen and sulfur;

or a pharmaceutically acceptable salt thereof.

Pharmacology

The compounds of formula (I) are active as cdk/cyclin inhibitors and are therefore useful to restrict the unregulated proliferation of tumor cells, hence in therapy in the treatment of various tumors such as, for instance, carcinomas, e.g. mammary carcinoma, lung carcinoma, bladder carcinoma, colon carcinoma, ovary and endometrial tumors, sarcomas, e.g. soft tissue and bone sarcomas, and the hematological malignancies such as, e.g., leukemias.

In addition, the compounds of formula (I) are also useful in the treatment of other cell proliferative disorders such as psoriasis, vascular smooth cell proliferation associated with atherosclerosis and post-surgical stenosis and restenosis and in the treatment of Alzheimer's disease.

The inhibiting activity of putative protein kinase inhibitors and the potency of selected compounds was determined through a method of assay based on the use of the MultiScreen-PH 96 well plate (Millipore), in which a phosphocellulose filter paper was placed at each well

bottom allowing binding of positive charged substrate after a washing/filtration step.

When a radioactivity labeled phosphate moiety was transferred by the ser/threo kinase to the filter-bound histone, light emitted was measured in a scintillation counter.

Inhibition assay of cdk2/Cyclin A activity

Kinase reaction: 1.5 µM histone H1 substrate, 25 µM ATP (0.2 uCi P33γ-ATP), 30 ng of baculovirus co-expressed cdk2/Cyclin A, 10 µM inhibitor in a final volume of 100 µl buffer (TRIS HCl 10 mM pH 7.5, $MgCl_2$ 10 mM, 7.5 mM DTT) were added to each well of a 96 U bottom well plate. After 10 min at 37 °C incubation, reaction was stopped by 20 µl EDTA 120 mM.

Capture: 100 µl were transferred from each well to MultiScreen plate, to allow substrate binding to phosphocellulose filter. Plates were then washed 3 times with 150 µl/well PBS Ca++/Mg++ free and filtered by MultiScreen filtration system.

Detection: filters were allowed to dry at 37°C, then 100 µl/well scintillant were added and 33P labeled histone H1 was detected by radioactivity counting in the Top-Count instrument.

Results: data were analyzed and expressed as % inhibition referred to total activity of enzyme (=100%).

All compounds showing inhibition $\geq$ 50 % were further analyzed in order to study and define potency (IC50) as well as the kinetic-profile of inhibitor through Ki calculation.

IC50 determination: the protocol used was the same described above, where inhibitors were tested at different concentrations ranging from 0.0045 to 10 µM. Experimental

data were analyzed by the computer program GraphPad Prizm using the four parameter logistic equation:

y = bottom+(top-bottom)/(1+10^((logIC50-x)*slope))

where x is the logarithm of the inhibitor concentration, y is the response; y starts at bottom and goes to top with a sigmoid shape.

Ki calculation: either the concentration of ATP and histone H1 substrate were varied: 4, 8, 12, 24, 48 μM for ATP (containing proportionally diluted $P^{33}\gamma$-ATP) and 0.4, 0.8, 1.2, 2.4, 4.8 μM for histone were used in absence and presence of two different, properly chosen inhibitor concentrations.

Experimental data were analyzed by the computer program "SigmaPlot" for Ki determination, using a random bireactant system equation:

$$v = \frac{Vmax \frac{(A)(B)}{aKAKB}}{1 + \frac{(A)}{KA} + \frac{(B)}{KB} + \frac{(A)(B)}{aKAKB}}$$

where A=ATP and B=histone H1.

In addition the selected compounds have been characterized on a panel of ser/threo kinases strictly related to cell cycle (cdk2/cyclin E, cdk1/cyclin B1, cdk4/Cyclin D1), and also for specificity on MAPK, PKA, EGFR, IGF1-R, Cdc7/dbf4 and aurora-2.

Inhibition assay of cdk2/Cyclin E activity

Kinase reaction: 1.5 μM histone H1 (Sigma # H-5505) substrate, 25 μM ATP (0.2 μCi $P^{33}\gamma$-ATP), 15 ng of baculovirus co-expressed cdk2/GST-Cyclin E, suitable

concentrations of inhibitor in a final volume of 100 µl buffer (TRIS HCl 10 mM pH 7.5, $MgCl_2$ 10 mM, 7.5 mM DTT+ 0.2mg/ml BSA) were added to each well of a 96 U bottom well plate. After 10 min at 37 °C incubation, reaction was stopped by 20 µl EDTA 120 mM.

Capture: 100 µl were transferred from each well to MultiScreen plate, to allow substrate binding to phosphocellulose filter. Plates were then washed 3 times with 150 µl/well PBS Ca^{++}/Mg^{++} free and filtered by MultiScreen filtration system.

Detection: filters were allowed to dry at 37°C, then 100 µl/well scintillant were added and ^{33}P labeled histone H1 was detected by radioactivity counting in the Top-Count instrument.

Inhibition assay of cdk1/Cyclin B1 activity

Kinase reaction: 1.5 µM histone H1 (Sigma # H-5505) substrate, 25 µM ATP (0.2 µCi $P^{33}\gamma$-ATP), 30 ng of baculovirus co-expressed cdk1/Cyclin B1, suitable concentrations of inhibitor in a final volume of 100 µl buffer (TRIS HCl 10 mM pH 7.5, $MgCl_2$ 10 mM, 7.5 mM DTT+ 0.2mg/ml BSA) were added to each well of a 96 U bottom well plate. After 10 min at 37 °C incubation, reaction was stopped by 20 µl EDTA 120 mM.

Capture: 100 µl were transferred from each well to MultiScreen plate, to allow substrate binding to phosphocellulose filter. Plates were then washed 3 times with 150 µl/well PBS Ca^{++}/Mg^{++} free and filtered by MultiScreen filtration system.

Detection: filters were allowed to dry at 37°C, then 100 µl/well scintillant were added and ^{33}P labeled histone H1 was detected by radioactivity counting in the Top-Count instrument.

Inhibition assay cdk4/Cyclin D1 activity

Kinase reaction: 0,4 uM μM mouse GST-Rb(769-921) (# sc-4112 from Santa Cruz) substrate, 10 μM ATP (0.5 μCi $P^{33}\gamma$-ATP), 100 ng of baculovirus expressed GST-cdk4/GST-Cyclin D1, suitable concentrations of inhibitor in a final volume of 50 μl buffer (TRIS HCl 10 mM pH 7.5, $MgCl_2$ 10 mM, 7.5 mM DTT+ 0.2mg/ml BSA) were added to each well of a 96 U bottom well plate. After 40 min at 37 °C incubation, reaction was stopped by 20 μl EDTA 120 mM.

Capture: 60 μl were transferred from each well to MultiScreen plate, to allow substrate binding to phosphocellulose filter. Plates were then washed 3 times with 150 μl/well PBS Ca^{++}/Mg^{++} free and filtered by MultiScreen filtration system.

Detection: filters were allowed to dry at 37°C, then 100 μl/well scintillant were added and ^{33}P labeled Rb fragment was detected by radioactivity counting in the Top-Count instrument.

Inhibition assay of MAPK activity

Kinase reaction: 10 μM MBP (Sigma # M-1891) substrate, 25 μM ATP (0.2 μCi $P^{33}\gamma$-ATP), 25 ng of bacterially expressed GST-MAPK (Upstate Biotechnology # 14-173), suitable concentrations of inhibitor in a final volume of 100 μl buffer (TRIS HCl 10 mM pH 7.5, $MgCl_2$ 10 mM, 7.5 mM DTT + 0.1 mg/ml BSA) were added to each well of a 96 U bottom well plate. After 15 min at 37 °C incubation, reaction was stopped by 20 μl EDTA 120 mM.

Capture: 100 μl were transferred from each well to MultiScreen plate, to allow substrate binding to phosphocellulose filter. Plates were then washed 3 times

with 150 µl/well PBS Ca^{++}/Mg^{++} free and filtered by MultiScreen filtration system.

Detection: filters were allowed to dry at 37°C, then 100 µl/well scintillant were added and ^{33}P labeled MBP was detected by radioactivity counting in the Top-Count instrument.

Inhibition assay of PKA activity

Kinase reaction: 10 µM histone H1 (Sigma # H-5505) substrate, 10 µM ATP (0.2 µCi $P^{33}\gamma$-ATP), 1U of bovine heart PKA (Sigma # 2645), suitable concentrations of inhibitor in a final volume of 100 µl buffer (TRIS HCl 10 mM pH 7.5, $MgCl_2$ 10 mM, 7.5 mM DTT+ 0.2mg/ml BSA) were added to each well of a 96 U bottom well plate. After 5 min at 37 °C incubation, reaction was stopped by 20 µl EDTA 120 mM.

Capture: 100 µl were transferred from each well to MultiScreen plate, to allow substrate binding to phosphocellulose filter. Plates were then washed 3 times with 150 µl/well PBS Ca^{++}/Mg^{++} free and filtered by MultiScreen filtration system.

Detection: filters were allowed to dry at 37°C, then 100 µl/well scintillant were added and ^{33}P labeled histone H1 was detected by radioactivity counting in the Top-Count instrument.

Inhibition assay of EGFR activity

Kinase reaction: 25 nM in house biotinylated PolyGluTyr (Sigma # 0275) substrate, 2,5 µM ATP (0.3 µCi $P^{33}\gamma$-ATP), 80 ng baculovirus expressed GST-EGFR, suitable concentrations of inhibitor in a final volume of 100 µl buffer (Hepes 50 mM pH 7,5, $MnCl_2$- $MgCl_2$ 3mM, 1mM DTT + 3 µM NaVO3, 0.1 mg/ml

BSA) were added to each well of a 96 U bottom well plate. After 5 min. at 37 °C incubation, reaction was stopped by 20 µl EDTA 120 mM.

Capture: 100 µl were transferred from each well to streptavidin-Flashplate, to allow biotinylated-substrate binding to plate. Plates were then washed 3 times with 150 µl/well PBS Ca^{++}/Mg^{++} free.

Detection: radioactivity counting in the Top-Count instrument.

Inhibition assay of IGF1-R activity

The inhibition assay of IGF1-R activity was performed according to the following protocol.

Kinase reaction: 10 µM biotinylated MBP (Sigma cat. # M-1891) substrate, 0-20 µM inhibitor, 6 µM cold ATP, 2 nM ^{33}P-ATP, and 22.5 ng IGF1-R (pre-incubated for 30 min at room temperature with cold 60 µM cold ATP) in a final volume of 30 µl buffer (50 mM HEPES pH 7.9, 3 mM $MnCl_2$, 1 mM DTT, 3 µM $NaVO_3$) were added to each well of a 96 U bottom well plate. After incubation for 35 min at room temperature, the reaction was stopped by addition of 100 µl PBS buffer containing 32 mM EDTA, 500 µM cold ATP, 0.1% Triton X100 and 10mg/ml streptavidin coated SPA beads. After 15 min incubation, 110 µL of suspension were withdrawn and transferred into 96-well OPTIPLATEs containing 100 µl of 5M CsCl. After 4 hours, the plates were read for 2 min in a Packard TOP-Count radioactivity reader.

Results: Experimental data were analyzed with the program GraphPad Prizm.

In addition, the inhibiting activity of putative protein kinase inhibitors and the potency of selected compounds was also determined through a method of assay based on the use of a SPA (Scintillation Proximity Assay) 96 well plate assay. The assay is based on the ability of streptavidin coated SPA beads to capture a biotinylated peptide derived from a phosphorylation site of histone.

When a radioactivity labeled phosphate moiety was transferred by the ser/threo kinase to the biotinylated histone peptide, light emitted was measured in a scintillation counter.

Inhibition assay of cdk5/p25 activity

The inhibition assay of cdk5/p25 activity was performed according to the following protocol.

Kinase reaction: 1.0 µM biotinylated histone peptide substrate, 0.25 uCi P33g-ATP, 4 nM cdk5/p25 complex, 0-100 µM inhibitor in a final volume of 100 µl buffer (Hepes 20 mM pH 7.5, MgCl2 15 mM, 1 mM DTT) were added to each well of a 96 U bottom well plate. After 20 min at 37 °C incubation, the reaction was stopped by the addition of 500 ug SPA beads in phosphate-buffered saline containing 0.1% Triton X-100, 50 uM ATP and 5 mM EDTA. The beads were allowed to settle, and the radioactivity incorporated in the 33P-labelled peptide was detected in a Top Count scintillation counter.

Results: Data were analyzed and expressed as % Inhibition using the formula:

100X(1 - (Unknown - Bkgd)/(Enz. Control - Bkgd))

IC50 values were calculated using a variation of the four parameter logistics equation:

Y = 100/[1 + 10 ^((LogEC50 - X)*Slope)]

Where X =log(uM) and Y = % Inhibition.

Inhibition assay of Cdc7/dbf4 activity

The inhibition assay of Cdc7/dbf4 activity was performed according to the following protocol.

The Biotin-MCM2 substrate is trans-phosphorylated by the Cdc7/Dbf4 complex in the presence of ATP traced with γ^{33}-ATP. The phosphorylated Biotin-MCM2 substrate is then captured by Streptavidin-coated SPA beads and the extent of phosphorylation evaluated by β counting.

The inhibition assay of Cdc7/dbf4 activity was performed in 96 wells plate according to the following protocol.

To each well of the plate were added :

- 10 µl substrate (biotinylated MCM2, 6 µM final concentration)
- 10 µl enzyme (Cdc7/Dbf4, 12.5 nM final concentration)
- 10 µl test compound (12 increasing concentrations in the nM to µM range to generate a dose-response curve)
- 10 µl of a mixture of cold ATP (10µM final concentration) and radioactive ATP (1/2500 molar ratio with cold ATP) was then used to start the reaction which was allowed to take place at 37°C.

Substrate, enzyme and ATP were diluted in 50 mM HEPES pH 7.9 containing 15 mM $MgCl_2$, 2 mM DTT, 3 µM $NaVO_3$, 2mM glycerophosphate and 0.2mg/ml BSA. The solvent for test compounds also contained 10% DMSO.

After incubation for 20 minutes, the reaction was stopped by adding to each well 100 µl of PBS pH 7.4 containing 50 mM EDTA, 1 mM cold ATP, 0.1% Triton X100 and 10 mg/ml streptavidin coated SPA beads.

After 15 minutes of incubation at room temperature to allow the biotinylated MCM2-streptavidin SPA beads interaction to occur, beads were trapped in a 96 wells filter plate (Unifilter^{R} GF/B^{TM}) using a Packard Cell Harvester

(Filtermate), washed with distilled water and then counted using a Top Count (Packard).

Counts were blank-subtracted and then the experimental data (each point in triplicate) were analyzed for IC50 determination using a non-linear regression analysis (Sigma Plot).

Inhibition assay of aurora-2 activity

The inhibiting activity and the potency of selected compounds was determined through a method of assay based on the use of the streptavidin scintillation proximity assay beads (amershampharmacia biotech) run in a 96 well plates. At the end of the reaction, the biotinylated peptide substrate was captured with the beads and subsequently allowed to stratify using $CsCl_2$.

When a radioactivity labeled phosphate moiety was transferred by the kinase to the beads-bound peptide, light emitted was measured in a scintillation counter.

The inhibition assay of Aurora-2 activity was performed in 96 wells plate according to the following protocol.

Kinase reaction: 8 μM biotinylated peptide (4 repeats of LRRWSLG), 10 μM ATP (0.5 uCi $P^{33}g$-ATP), 10 nM Aurora2, 10 μM inhibitor in a final volume of 60 μl buffer (HEPES 50 mM pH 7.0, $MgCl_2$ 10 mM, 1 mM DTT, 0.125 mg/ml BSA, 3μM orthovanadate) were added to each well of a 96 U bottom well plate. After 30 minutes at room temperature incubation, reaction was stopped and biotinylated peptide captured by adding 100 μl of bead suspension.

Stratification: 100 μl of CsCl2 7.5 M were added to each well and let stand one hour before radioactivity was counted in the Top-Count instrument.

Results: data were analyzed and expressed as % inhibition referred to total activity of enzyme (=100%).

All compounds showing inhibition $\geq$ 60 % were further analyzed in order to study the potency of the inhibitor through IC50 calculation.

The protocol used was the same described above, except that serial dilution of the inhibitor was used. Experimental data were fitted by nonlinear regression using the following equation:

$$v = v_0 + \frac{(v_0 - v_b)}{1 + 10^{n(\log IC_{50} - \log[I])}}$$

With v_b as the baseline velocity, v as the observed reaction velocity, v_o as the velocity in the absence of inhibitors, and [I] as the inhibitor concentration.

The compounds of formula (I) of the present invention, suitable for administration to a mammal, e.g. to humans, can be administered by the usual routes and the dosage level depends upon the age, weight, conditions of the patient and the administration route.

For example, a suitable dosage adopted for oral administration of a compound of formula (I) may range from about 10 to about 500 mg pro dose, from 1 to 5 times daily. The compounds of the invention can be administered in a variety of dosage forms, e.g. orally, in the form of tablets, capsules, sugar or film coated tablets, liquid solutions or suspensions; rectally in the form of suppositories; parenterally, e.g. intramuscularly, or by intravenous and/or intrathecal and/or intraspinal injection or infusion.

In addition, the compounds of the invention can be administered either as single agents or, alternatively, in combination with known anticancer treatments such as

radiation therapy or chemotherapy regimen in combination with cytostatic or cytotoxic agents, antibiotic-type agents, alkylating agents, antimetabolite agents, hormonal agents, immunological agents, interferon-type agents, cyclooxygenase inhibitors (e.g. COX-2 inhibitors), metallomatrixprotease inhibitors, telomerase inhibitors, tyrosine kinase inhibitors, anti-growth factor receptor agents, anti-HER agents, anti-EGFR agents, anti-angiogenesis agents, farnesyl transferase inhibitors, ras-raf signal transduction pathway inhibitors, cell cycle inhibitors, other cdks inhibitors, tubulin binding agents, topoisomerase I inhibitors, topoisomerase II inhibitors, and the like.

As an example, the compounds of the invention can be administered in combination with one or more chemotherapeutic agents such as, for instance, taxane, taxane derivatives, encapsulated taxanes, CPT-11, camptothecin derivatives, anthracycline glycosides, e.g., doxorubicin, idarubicin, epirubicin, etoposide, navelbine, vinblastine, carboplatin, cisplatin, estramustine, celecoxib, Sugen SU-5416, Sugen SU-6668, Herceptin, and the like, optionally within liposomal formulations thereof.

If formulated as a fixed dose, such combination products employ the compounds of this invention within the dosage range described above and the other pharmaceutically active agent within the approved dosage range.

Compounds of formula (I) may be used sequentially with known anticancer agents when a combination formulation is inappropriate.

The present invention also includes pharmaceutical compositions comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof in association with a pharmaceutically acceptable excipient (which can be a carrier or a diluent).

The pharmaceutical compositions containing the compounds of the invention are usually prepared following conventional methods and are administered in a pharmaceutically suitable form.

For example, the solid oral forms may contain, together with the active compound, diluents, e.g. lactose, dextrose, saccharose, sucrose, cellulose, corn starch or potato starch; lubricants, e.g. silica, talc, stearic , magnesium or calcium stearate, and/or polyethylene glycols; binding agents, e.g. starches, arabic gum, gelatin, methylcellulose, carboxymethylcellulose or polyvinyl pyrrolidone; disaggregating agents, e.g. a starch, alginic , alginates or sodium starch glycolate; effervescing mixtures; dyestuffs; sweeteners; wetting agents such as lecithin, polysorbates, laurylsulfates; and, in general, non-toxic and pharmacologically inactive substances used in pharmaceutical formulations. Said pharmaceutical preparations may be manufactured in known manner, for example, by means of mixing, granulating, tabletting, sugar-coating, or film-coating processes.

The liquid dispersions for oral administration may be e.g. syrups, emulsions and suspensions.

The syrups may contain as carrier, for example, saccharose or saccharose with glycerin and/or mannitol and/or sorbitol.

The suspensions and the emulsions may contain as carrier, for example, a natural gum, agar, sodium alginate, pectin, methylcellulose, carboxymethylcellulose, or polyvinyl alcohol.

The suspension or solutions for intramuscular injections may contain, together with the active compound, a pharmaceutically acceptable carrier, e.g. sterile water, olive oil, ethyl oleate, glycols, e.g. propylene glycol, and, if desired, a suitable amount of lidocaine hydrochloride. The solutions for intravenous injections or

infusions may contain as carrier, for example, sterile water or preferably they may be in the form of sterile, aqueous, isotonic saline solutions or they may contain as a carrier propylene glycol.

The suppositories may contain together with the active compound a pharmaceutically acceptable carrier, e.g. cocoa butter, polyethylene glycol, a polyoxyethylene sorbitan fatty ester surfactant or lecithin.

The following examples illustrate but do not limit the present invention.

Example 1

Preparation of N-[3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thien-2-yl]phenylacetamide (Compound 1)

A mixture of commercially available 2-amino-3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thiophene (5 mg, 0.026 mmol), phenylacetic acid (7 mg, 0.05 mmol), N-hydroxybenzotriazole (8.5 mg, 0.065 mmol), and N-cyclohexylcarbodiimide-N'-methylpolystyrene (loading about 1.5 mmol/g resin, 50 mg) in dichloromethane (2ml)/dimethylformamide (0.5 ml) was agitated at 20°C for 170 h. Afterward tris-(2-aminoethyl)-amine polystyrene (loading about 4 mmol/g resin 40 mg) was added for scavenging the hydroxybenzotriazole and the excess of acid, and the agitation was maintained for additional 24 h.

The resins were filtered, washed with dichloromethane, and the resulting solution was evaporated to give 15 mg of crude material. The reaction mixture was purified by preparative high-pressure liquid chromatography using the following conditions:

Eluent A : aqueous solution of trifluoroacetic acid (0.01% v/v)

Eluent B : acetonitrile

Gradient :	Time (m)	%A	%B
0	(injection)	90	10
8		10	90
10	(end)	10	90

Flow : 20 ml/m
Column: Waters Symmetry™ C18 19 x 50 mm
Detector: mass spectrometer, electrospray ionization, positive mode.

A liquid handler triggered by the mass spectrometer automatically collected the fractions containing the title compound. After evaporation of the solvent 3.4 mg of N-[3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thien-2-yl]phenylacetamide (colorless solid, $[M+H]^+$ = 315) were obtained.

Analogously, by reacting the 3-amino-thiophene derivative of formula (II), as reported in table I, each of which easily obtainable from the commercially available carboxylic ester, with the commercially available carboxylic acids of formula (III), reported in table II, a library of N-[3-carbamoyl-4,5-substituted-thien-2-yl] amides of formula (I) was thus prepared.
Representative compounds of the library are reported in table III.

Table III: representative library compounds:

n°	Compound	$[M+H]^+$
2	N-[3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thien-2-yl]acetamide;	239
3	N-[3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thien-2-yl]propionamide;	253

4	N-[3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thien-2-yl]2-butynoic amide;	263
5	N-[3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thien-2-yl]cyanoacetamide;	267
6	N-[3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thien-2-yl]cyclopropanecarboxamide;	265
7	N-[3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thien-2-yl]isobutyramide;	267
8	N-[3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thien-2-yl]3,3-dimethylacrylic amide;	279
9	N-[3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thien-2-yl]2-ketobutyramide;	281
10	N-[3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thien-2-yl]N,N-dimethylglycinamide;	282
11	N-[3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thien-2-yl]3-chloropropionamide;	287
12	N-[3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thien-2-yl]imidazol-4-carboxamide;	291
13	N-[3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thien-2-yl]pyrrole-2-carboxamide;	290
14	N-[3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thien-2-yl]cyclopentanecarboxamide;	293
15	N-[3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thien-2-yl]1-cyanocyclopropanecarboxamide;	290
16	N-[3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thien-2-yl]N-acetylglycinamide;	296
17	N-[3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thien-2-yl]pyrrole-3-carboxamide;	290
18	N-[3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thien-2-yl]benzamide;	301
19	N-[3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thien-2-yl]4-pyrazolecarboxamide;	291
20	N-[3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thien-2-yl]picolinic amide;	302
21	N-[3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thien-2-yl]nicotinic amide;	302

22	N-[3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thien-2-yl]isonicotinic amide;	302
23	N-[3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thien-2-yl]2-pyrazinecarboxamide;	303
24	N-[3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thien-2-yl]1-methylpyrrole-2-carboxamide;	304
25	N-[3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thien-2-yl]3-methyl-2-furoic amide;	305
26	N-[3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thien-2-yl]5-methylisoxazole-4-carboxamide;	306
27	N-[3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thien-2-yl]3-methylisoxazole-4-carboxamide;	306
28	N-[3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thien-2-yl]thiophene-2-carboxamide;	307
29	N-[3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thien-2-yl]thiophene-3-carboxamide;	307
30	N-[3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thien-2-yl]dl-pyroglutamic amide;	308
31	N-[3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thien-2-yl]1-(aminocarbonyl)-1-cyclopropanecarboxamide;	308
32	N-[3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thien-2-yl]o-toluic amide;	315
33	N-[3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thien-2-yl]5-methylisoxazole-3-carboxamide;	306
34	N-[3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thien-2-yl]m-toluic amide;	315
35	N-[3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thien-2-yl]3-aminopyrazole-4-carboxamide;	306
36	N-[3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thien-2-yl]p-toluic amide;	315
37	N-[3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thien-2-yl]salicylic amide;	317
38	N-[3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thien-2-yl]3-hydroxybenzamide;	317
39	N-[3-carbamoyl-5-isopropyl-thien-2-yl]cyclopentylacetamide;	295

40	N-[3-carbamoyl-5-isopropyl-thien-2-yl]4-hydroxybenzamide;	305
41	N-[3-carbamoyl-5-isopropyl-thien-2-yl]5-norbornene-2-carboxamide;	305
42	N-[3-carbamoyl-5-isopropyl-thien-2-yl]2-fluorobenzamide;	307
43	N-[3-carbamoyl-5-isopropyl-thien-2-yl]2-imidazolidone-4-carboxamide;	297
44	N-[3-carbamoyl-5-isopropyl-thien-2-yl]3-fluorobenzamide;	307
45	N-[3-carbamoyl-5-isopropyl-thien-2-yl]N'-acetyl-dl-alaninamide;	298
46	N-[3-carbamoyl-5-isopropyl-thien-2-yl]4-fluorobenzamide;	307
47	N-[3-carbamoyl-5-isopropyl-thien-2-yl]3-ureidopropionamide;	299
48	N-[3-carbamoyl-5-isopropyl-thien-2-yl]thiophene-2-acetamide;	309
49	N-[3-carbamoyl-5-isopropyl-thien-2-yl]thiophene-3-acetamide;	309
50	N-[3-carbamoyl-5-isopropyl-thien-2-yl]3-cyclopentylpropionamide;	309
51	N-[3-carbamoyl-5-isopropyl-thien-2-yl]cycloheptanecarboxamide;	309
52	N-[3-carbamoyl-5-isopropyl-thien-2-yl]2,2-dimethylhexanoic amide;	311
53	N-[3-carbamoyl-5-isopropyl-thien-2-yl]alpha-(isopropylideneaminooxy)propionamide;	312
54	N-[3-carbamoyl-5-isopropyl-thien-2-yl]N,N-dimethylsuccinamic amide;	312
55	N-[3-carbamoyl-5-isopropyl-thien-2-yl]urocanic amide;	305
56	N-[3-carbamoyl-5-isopropyl-thien-2-yl]phenylpropiolic amide;	313
57	N-[3-carbamoyl-5-isopropyl-thien-2-yl]2-methylpyrazine-5-carboxamide;	305
58	N-[3-carbamoyl-5-isopropyl-thien-2-yl]3-cyanobenzamide;	314
59	N-[3-carbamoyl-5-isopropyl-thien-2-yl]4-cyanobenzamide;	314
60	N-[3-carbamoyl-5-isopropyl-thien-2-yl]N-methyl-l-proline monohydrate;	296
61	N-[3-carbamoyl-5-isopropyl-thien-2-yl]cinnamic amide;	315
62	N-[3-carbamoyl-5-isopropyl-thien-2-yl]3-(3-pyridyl)acrylic amide;	316
63	N-[3-carbamoyl-5-isopropyl-thien-2-yl]3,5-dimethylisoxazole-4-carboxamide;	308
64	N-[3-carbamoyl-5-isopropyl-thien-2-yl]3-(4-pyridyl)-acrylic amide;	316

65	N-[3-carbamoyl-5-isopropyl-thien-2-yl]2,3-dimethylbenzamide;	317
66	N-[3-carbamoyl-5-isopropyl-thien-2-yl]2,4-dimethylbenzamide;	317
67	N-[3-carbamoyl-5-isopropyl-thien-2-yl]2,5-dimethylbenzamide;	317
68	N-[3-carbamoyl-5-isopropyl-thien-2-yl]2,6-dimethylbenzamide;	317
69	N-[3-carbamoyl-5-isopropyl-thien-2-yl]3,4-dimethylbenzamide;	317
70	N-[3-carbamoyl-5-isopropyl-thien-2-yl]3,5-dimethylbenzamide;	317
71	N-[3-carbamoyl-5-isopropyl-thien-2-yl]2-phenylpropionamide;	317
72	N-[3-carbamoyl-5-isopropyl-thien-2-yl]3-phenylpropionamide;	317
73	N-[3-carbamoyl-5-isopropyl-thien-2-yl]N-carbamyl-dl-alpha-amino-n-butyramide;	313
74	N-[3-carbamoyl-5-isopropyl-thien-2-yl]o-tolylacetamide;	317
75	N-[3-carbamoyl-5-isopropyl-thien-2-yl]m-tolylacetamide;	317
76	N-[3-carbamoyl-5-isopropyl-thien-2-yl]p-tolylacetamide;	317
77	N-[3-carbamoyl-5-isopropyl-thien-2-yl]3-pyridinepropionamide;	318
78	N-[3-carbamoyl-5-phenyl-thien-2-yl]o-anisic amide;	353
79	N-[3-carbamoyl-5-phenyl-thien-2-yl]3-methylsalicylic amide;	353
80	N-[3-carbamoyl-5-phenyl-thien-2-yl]4-methylsalicylic amide;	353
81	N-[3-carbamoyl-5-phenyl-thien-2-yl]5-methylsalicylic amide;	353
82	N-[3-carbamoyl-5-phenyl-thien-2-yl]3-methoxybenzamide;	353
83	N-[3-carbamoyl-5-phenyl-thien-2-yl]3-hydroxy-4-methylbenzamide;	353
84	N-[3-carbamoyl-5-phenyl-thien-2-yl]p-anisic amide;	353
85	N-[3-carbamoyl-5-phenyl-thien-2-yl]phenoxyacetamide;	353
86	N-[3-carbamoyl-5-phenyl-thien-2-yl]2-hydroxyphenylacetamide;	353
87	N-[3-carbamoyl-5-phenyl-thien-2-yl]3-hydroxyphenylacetamide;	353
88	N-[3-carbamoyl-5-phenyl-thien-2-yl]4-hydroxyphenylacetamide;	353
89	N-[3-carbamoyl-5-phenyl-thien-2-yl]dl-mandelic amide;	353

90	N-[3-carbamoyl-5-phenyl-thien-2-yl]3-hydroxy-o-toluic amide;	353
91	N-[3-carbamoyl-5-phenyl-thien-2-yl]alpha-fluorophenylacetamide;	355
92	N-[3-carbamoyl-5-phenyl-thien-2-yl]2-fluorophenylacetamide;	355
93	N-[3-carbamoyl-5-phenyl-thien-2-yl]3-fluorophenylacetamide;	355
94	N-[3-carbamoyl-5-phenyl-thien-2-yl]4-fluorophenylacetamide;	355
95	N-[3-carbamoyl-5-phenyl-thien-2-yl]3-(2-thienyl)acrylic amide;	355
96	N-[3-carbamoyl-5-phenyl-thien-2-yl]3-(3-thienyl)-acrylic amide;	355
97	N-[3-carbamoyl-5-phenyl-thien-2-yl]3-(2-thienyl)propanoic amide;	357
98	N-[3-carbamoyl-5-phenyl-thien-2-yl]2-chlorobenzamide;	357
99	N-[3-carbamoyl-5-phenyl-thien-2-yl]3-chlorobenzamide;	357
100	N-[3-carbamoyl-5-phenyl-thien-2-yl]4-chlorobenzamide;	357
101	N-[3-carbamoyl-5-phenyl-thien-2-yl]N-propylmaleamic amide;	358
102	N-[3-carbamoyl-5-phenyl-thien-2-yl]N'-acetyl-dl-allylglycinamide;	358
103	N-[3-carbamoyl-5-phenyl-thien-2-yl]N'-acetyl-dl-prolinamide;	358
104	N-[3-carbamoyl-5-phenyl-thien-2-yl]3-(1-piperidine)propionamide;	358
105	N-[3-carbamoyl-5-phenyl-thien-2-yl]2-chloronicotinic amide;	358
106	N-[3-carbamoyl-5-phenyl-thien-2-yl]6-chloronicotinic amide;	358
107	N-[3-carbamoyl-5-phenyl-thien-2-yl]N-(acetoacetyl)glycinamide;	360
108	N-[3-carbamoyl-5-phenyl-thien-2-yl]N'-acetyl-dl-valinamide;	360
109	N-[3-carbamoyl-5-phenyl-thien-2-yl]dl-alanyl-dl-alanine;	361
110	N-[3-carbamoyl-5-phenyl-thien-2-yl]indole-6-carboxamide;	362
111	N-[3-carbamoyl-5-phenyl-thien-2-yl]benzofuran-2-carboxamide;	363
112	N-[3-carbamoyl-5-phenyl-thien-2-yl]1-phenyl-1-cyclopropanecarboxamide;	363
113	N-[3-carbamoyl-5-phenyl-thien-2-yl]cycloheptylacetamide;	357
114	N-[3-carbamoyl-5-phenyl-thien-2-yl]alpha-methylcinnamic amide;	363

115	N-[3-carbamoyl-5-phenyl-thien-2-yl]2-acetylbenzamide;	365
116	N-[3-carbamoyl-5-benzyl-thien-2-yl]4-acetylbenzamide;	379
117	N-[3-carbamoyl-5-benzyl-thien-2-yl]o-coumaric amide;	379
118	N-[3-carbamoyl-5-benzyl-thien-2-yl]3-hydroxycinnamic amide;	379
119	N-[3-carbamoyl-5-benzyl-thien-2-yl]4-hydroxycinnamic amide;	379
120	N-[3-carbamoyl-5-benzyl-thien-2-yl]p-coumaric amide;	379
121	N-[3-carbamoyl-5-benzyl-thien-2-yl]4-isopropylbenzamide;	379
122	N-[3-carbamoyl-5-benzyl-thien-2-yl]2-(3,5-xylyl)acetamide;	379
123	N-[3-carbamoyl-5-benzyl-thien-2-yl]phthalamic amide;	380
124	N-[3-carbamoyl-5-benzyl-thien-2-yl]N-carbamoylmaleamic amide;	373
125	N-[3-carbamoyl-5-benzyl-thien-2-yl]3-dimethylaminobenzamide;	380
126	N-[3-carbamoyl-5-benzyl-thien-2-yl]4-dimethylaminobenzamide;	380
127	N-[3-carbamoyl-5-benzyl-thien-2-yl]2-dimethylaminobenzamide;	380
128	N-[3-carbamoyl-5-benzyl-thien-2-yl]N'-carbamyl-dl-norvalinamide;	375
129	N-[3-carbamoyl-5-benzyl-thien-2-yl]piperonylic amide;	381
130	N-[3-carbamoyl-5-benzyl-thien-2-yl]N-carbamyl-dl-valine;	375
131	N-[3-carbamoyl-5-benzyl-thien-2-yl]alpha-fluorocinnamic amide;	381
132	N-[3-carbamoyl-5-benzyl-thien-2-yl]3-methoxy-4-methylbenzamide;	381
133	N-[3-carbamoyl-5-benzyl-thien-2-yl]indole-2-carboxamide;	376
134	N-[3-carbamoyl-5-benzyl-thien-2-yl]4-hydroxy-3,5-dimethylbenzamide;	381
135	N-[3-carbamoyl-5-benzyl-thien-2-yl]indole-3-carboxamide;	376
136	N-[3-carbamoyl-5-benzyl-thien-2-yl]benzyloxyacetamide;	381
137	N-[3-carbamoyl-5-benzyl-thien-2-yl]indole-5-carboxamide;	376
138	N-[3-carbamoyl-5-benzyl-thien-2-yl]4-dimethylaminobutyramide;	346
139	N-[3-carbamoyl-5-benzyl-thien-2-yl]indole-4-carboxamide;	376

140	N-[3-carbamoyl-5-benzyl-thien-2-yl]3-methoxysalicylic amide;	383
141	N-[3-carbamoyl-5-benzyl-thien-2-yl]4-methoxysalicylic amide;	383
142	N-[3-carbamoyl-5-benzyl-thien-2-yl]5-methoxysalicylic amide;	383
143	N-[3-carbamoyl-5-benzyl-thien-2-yl]5-benzimidazolecarboxamide;	377
144	N-[3-carbamoyl-5-benzyl-thien-2-yl]3-hydroxy-4-methoxybenzamide;	383
145	N-[3-carbamoyl-5-benzyl-thien-2-yl]indazole-3-carboxamide;	377
146	N-[3-carbamoyl-5-benzyl-thien-2-yl]vanillic amide;	383
147	N-[3-carbamoyl-5-benzyl-thien-2-yl]4-hydroxyphenoxyacetamide;	385
148	N-[3-carbamoyl-5-benzyl-thien-2-yl]6-methoxysalicylic amide;	383
149	N-[3-carbamoyl-5-benzyl-thien-2-yl]4-imidazoleacetamide;	341
150	N-[3-carbamoyl-5-benzyl-thien-2-yl]N-(2-furoyl)glycinamide;	384
151	N-[3-carbamoyl-5-benzyl-thien-2-yl]6-carboxypurine;	379
152	N-[3-carbamoyl-5-benzyl-thien-2-yl]beta-maleimidopropionamide;	384
153	N-[3-carbamoyl-5-benzyl-thien-2-yl]3,4-dihydro-2,2-dimethyl-4-oxo-2h-pyran-6-carboxamide;	385
154	N-[3-carbamoyl-5-(1-phenylethyl)-thien-2-yl]1-acetylpiperidine-4-carboxamide;	400
155	N-[3-carbamoyl-5-(1-phenylethyl)-thien-2-yl]1-naphthoic amide;	401
156	N-[3-carbamoyl-5-(1-phenylethyl)-thien-2-yl]2-naphthoic amide;	401
157	N-[3-carbamoyl-5-(1-phenylethyl)-thien-2-yl]4-chlorosalicylic amide;	401
158	N-[3-carbamoyl-5-(1-phenylethyl)-thien-2-yl]5-chlorosalicylic amide;	401
159	N-[3-carbamoyl-5-(1-phenylethyl)-thien-2-yl]3-chloro-4-hydroxybenzamide;	401
160	N-[3-carbamoyl-5-(1-phenylethyl)-thien-2-yl]3-chlorosalicylic amide;	401
161	N-[3-carbamoyl-5-(1-phenylethyl)-thien-2-yl]N'-acetyl-hydroxyproline;	402
162	N-[3-carbamoyl-5-(1-phenylethyl)-thien-2-yl]quinaldic amide;	402
163	N-[3-carbamoyl-5-(1-phenylethyl)-thien-2-yl]quinoline-3-carboxamide;	402

164	N-[3-carbamoyl-5-(1-phenylethyl)-thien-2-yl]quinoline-4-carboxamide;	402
165	N-[3-carbamoyl-5-(1-phenylethyl)-thien-2-yl]1-isoquinolinecarboxamide;	402
166	N-[3-carbamoyl-5-(1-phenylethyl)-thien-2-yl]quinoline-6-carboxamide;	402
167	N-[3-carbamoyl-5-(1-phenylethyl)-thien-2-yl]quinoline-8-carboxamide;	402
168	N-[3-carbamoyl-5-(1-phenylethyl)-thien-2-yl]6-acetamidohexanoic amide;	402
169	N-[3-carbamoyl-5-(1-phenylethyl)-thien-2-yl]N'-acetyl-dl-leucinamide;	402
170	N-[3-carbamoyl-5-(1-phenylethyl)-thien-2-yl]N',N'-di-n-propyl-l-alaninamide;	402
171	N-[3-carbamoyl-5-(1-phenylethyl)-thien-2-yl]N'-alpha-acetyl-l-asparaginamide;	403
172	N-[3-carbamoyl-5-(1-phenylethyl)-thien-2-yl]cinnoline-4-carboxamide;	403
173	N-[3-carbamoyl-5-(1-phenylethyl)-thien-2-yl]2-quinoxalinecarboxamide;	403
174	N-[3-carbamoyl-5-(1-phenylethyl)-thien-2-yl]3-methylindene-2-carboxamide;	403
175	N-[3-carbamoyl-5-(1-phenylethyl)-thien-2-yl]1-methylindole-2-carboxamide;	404
176	N-[3-carbamoyl-5-(1-phenylethyl)-thien-2-yl]1-methylindole-3-carboxamide;	404
177	N-[3-carbamoyl-5-(1-phenylethyl)-thien-2-yl]indazolone-4-carboxamide;	405
178	N-[3-carbamoyl-5-(1-phenylethyl)-thien-2-yl]3-oxo-1-indancarboxamide;	405
179	N-[3-carbamoyl-5-(1-phenylethyl)-thien-2-yl]1,2,3,4-tetrahydro-2-naphthoic amide;	405
180	N-[3-carbamoyl-5-(1-phenylethyl)-thien-2-yl]2-indanylacetamide;	405
181	N-[3-carbamoyl-5-(1-phenylethyl)-thien-2-yl]1-methyl-4-imidazole-acetamide;	369
182	N-[3-carbamoyl-5-(1-phenylethyl)-thien-2-yl]arecaidinamide;	370
183	N-[3-carbamoyl-5-(1-phenylethyl)-thien-2-yl]3-benzoylpropionamide;	407
184	N-[3-carbamoyl-5-(1-phenylethyl)-thien-2-yl]4-methoxycinnamic amide;	407
185	N-[3-carbamoyl-5-(1-phenylethyl)-thien-2-yl]2-methoxycinnamic amide;	407
186	N-[3-carbamoyl-5-(1-phenylethyl)-thien-2-yl]benzo[b]thiophene-2-carboxamide;	407
187	N-[3-carbamoyl-5-(1-phenylethyl)-thien-2-yl]2-isopropyl-2-phenylacetamide;	407
188	N-[3-carbamoyl-5-(1-phenylethyl)-thien-2-yl]N'-acetylanthranilic amide;	408

189	N-[3-carbamoyl-5-(1-phenylethyl)-thien-2-yl]4-acetamidobenzamide;	408
190	N-[3-carbamoyl-5-(1-phenylethyl)-thien-2-yl]hippuric amide;	408
191	N-[3-carbamoyl-5-(1-phenylethyl)-thien-2-yl]3-acetamidobenzamide;	408
192	N-[3-carbamoyl-4,5-dimethyl-thien-2-yl]3,4-methylenedioxyphenylacetamide;	333
193	N-[3-carbamoyl-4,5-dimethyl-thien-2-yl]nicotinuric amide;	333
194	N-[3-carbamoyl-4,5-dimethyl-thien-2-yl]4-isopropoxybenzamide;	333
195	N-[3-carbamoyl-4,5-dimethyl-thien-2-yl]3-(diethylamino)propionamide;	298
196	N-[3-carbamoyl-4,5-dimethyl-thien-2-yl]2,5-dimethoxybenzamide;	335
197	N-[3-carbamoyl-4,5-dimethyl-thien-2-yl]2,6-dimethoxybenzamide;	335
198	N-[3-carbamoyl-4,5-dimethyl-thien-2-yl]3,4-dimethoxybenzamide;	335
199	N-[3-carbamoyl-4,5-dimethyl-thien-2-yl]3,5-dimethoxybenzamide;	335
200	N-[3-carbamoyl-4,5-dimethyl-thien-2-yl]2-methoxyphenoxyacetamide;	335
201	N-[3-carbamoyl-4,5-dimethyl-thien-2-yl]1-thymineacetamide;	337
202	N-[3-carbamoyl-4,5-dimethyl-thien-2-yl]indole-3-acetamide;	328
203	N-[3-carbamoyl-4,5-dimethyl-thien-2-yl]3-(2-thenoyl)-propionamide;	337
204	N-[3-carbamoyl-4,5-dimethyl-thien-2-yl]3-chloro-4-methoxybenzamide;	339
205	N-[3-carbamoyl-4,5-dimethyl-thien-2-yl]5-methylindole-2-carboxamide;	328
206	N-[3-carbamoyl-4,5-dimethyl-thien-2-yl]5-chloro-2-methoxybenzamide;	339
207	N-[3-carbamoyl-4,5-dimethyl-thien-2-yl]1-(2-carboxyphenyl)pyrrole;	340
208	N-[3-carbamoyl-4,5-dimethyl-thien-2-yl]4-(1-H-pyrrol-1-yl)benzamide;	340
209	N-[3-carbamoyl-4,5-dimethyl-thien-2-yl]1-methyl-3-indoleacetamide;	342
210	N-[3-carbamoyl-4,5-dimethyl-thien-2-yl]2-methyl-1h-benzimidazole-5-carboxamide;	329
211	N-[3-carbamoyl-4,5-dimethyl-thien-2-yl]2-(trifluoromethyl)benzamide;	343
212	N-[3-carbamoyl-4,5-dimethyl-thien-2-yl]3-(trifluoromethyl)benzamide;	343
213	N-[3-carbamoyl-4,5-dimethyl-thien-2-yl]4-(trifluoromethyl)benzamide;	343

214	N-[3-carbamoyl-4,5-dimethyl-thien-2-yl]chromone-2-carboxamide;	343
215	N-[3-carbamoyl-4,5-dimethyl-thien-2-yl]5-hydroxyindole-2-carboxamide;	330
216	N-[3-carbamoyl-4,5-dimethyl-thien-2-yl]chromone-3-carboxamide;	343
217	N-[3-carbamoyl-4,5-dimethyl-thien-2-yl]3-hydroxy-2-quinoxalinecarboxamide;	343
218	N-[3-carbamoyl-4,5-dimethyl-thien-2-yl]1-phenyl-1-cyclopentanecarboxamide;	343
219	N-[3-carbamoyl-4,5-dimethyl-thien-2-yl]2,3-dichlorobenzamide;	344
220	N-[3-carbamoyl-4,5-dimethyl-thien-2-yl]2,4-dichlorobenzamide;	344
221	N-[3-carbamoyl-4,5-dimethyl-thien-2-yl]2,5-dichlorobenzamide;	344
222	N-[3-carbamoyl-4,5-dimethyl-thien-2-yl]2,6-dichlorobenzamide;	344
223	N-[3-carbamoyl-4,5-dimethyl-thien-2-yl]3,4-dichlorobenzamide;	344
224	N-[3-carbamoyl-4,5-dimethyl-thien-2-yl]3,5-dichlorobenzamide;	344
225	N-[3-carbamoyl-4,5-dimethyl-thien-2-yl]4-oxophenylamino-2-butenoic amide;	344
226	N-[3-carbamoyl-4,5-dimethyl-thien-2-yl]4-(dimethylamino)cinnamic amide;	344
227	N-[3-carbamoyl-4,5-dimethyl-thien-2-yl]N'-chloroacetyl-dl-2-amino-n-butyramide;	332
228	N-[3-carbamoyl-4,5-dimethyl-thien-2-yl]3,4-methylenedioxycinnamic amide;	345
229	N-[3-carbamoyl-4,5-dimethyl-thien-2-yl]7-methoxybenzofuran-2-carboxamide;	345
230	N-[3-carbamoyl-4,5-dimethyl-thien-2-yl]4-benzoylbutyramide;	345
231	N-[3-carbamoyl-4-methyl-thien-2-yl]benzo[b]thiophene-3-acetamide;	331
232	N-[3-carbamoyl-4-methyl-thien-2-yl]N'-benzoyl-beta-alaninamide;	332
233	N-[3-carbamoyl-4-methyl-thien-2-yl]N'-acetyl-dl-phenylglycinamide;	332
234	N-[3-carbamoyl-4-methyl-thien-2-yl]N'-benzoyl-dl-alaninamide;	332
235	N-[3-carbamoyl-4-methyl-thien-2-yl]N'-methylhippuric amide;	332
236	N-[3-carbamoyl-4-methyl-thien-2-yl]o-hydroxyhippuric amide;	334
237	N-[3-carbamoyl-4-methyl-thien-2-yl]N'-(furan-2-yl-acryl)-glycinamide;	334
238	N-[3-carbamoyl-4-methyl-thien-2-yl](3,5-dimethoxyphenyl)acetamide;	335

239	N-[3-carbamoyl-4-methyl-thien-2-yl]3,5-dimethoxy-4-methylbenzamide;	335
240	N-[3-carbamoyl-4-methyl-thien-2-yl](2,4-dimethoxy-phenyl)-acetamide;	335
241	N-[3-carbamoyl-4-methyl-thien-2-yl]5-(2-thienoyl)butyramide;	337
242	N-[3-carbamoyl-4-methyl-thien-2-yl]4-(methylsulfonyl)benzamide;	339
243	N-[3-carbamoyl-4-methyl-thien-2-yl]phenylsulfonylacetamide;	339
244	N-[3-carbamoyl-4-methyl-thien-2-yl]3-indolepropionamide;	328
245	N-[3-carbamoyl-4-methyl-thien-2-yl]3-(methylsulfonyl)benzamide;	339
246	N-[3-carbamoyl-4-methyl-thien-2-yl]2-methyl-3-indoleacetamide;	328
247	N-[3-carbamoyl-4-methyl-thien-2-yl]2-(methylsulfonyl)benzamide;	339
248	N-[3-carbamoyl-4-methyl-thien-2-yl]4-sulfonamidobenzamide;	340
249	N-[3-carbamoyl-4-methyl-thien-2-yl]5-methyl-1-phenylpyrazole-4-carboxamide;	341
250	N-[3-carbamoyl-4-methyl-thien-2-yl]5-methyl-3-phenylisoxazole-4-carboxamide;	342
251	N-[3-carbamoyl-4-methyl-thien-2-yl]2-hydroxy-5-(1 h-pyrrol-1-yl)benzamide;	342
252	N-[3-carbamoyl-4-methyl-thien-2-yl]4-methyl-2-phenyl-1,2,3-triazole-5-carboxamide;	342
253	N-[3-carbamoyl-4-methyl-thien-2-yl]N'-acetyl-dl-phenylglycinamide;	346
254	N-[3-carbamoyl-4-methyl-thien-2-yl]2,3-dimethoxycinnamic amide;	347
255	N-[3-carbamoyl-4-methyl-thien-2-yl]2-benzimidazolepropionamide;	329
256	N-[3-carbamoyl-4-methyl-thien-2-yl]2,5-dimethoxycinnamic amide;	347
257	N-[3-carbamoyl-4-methyl-thien-2-yl]3,4-dimethoxycinnamic amide;	347
258	N-[3-carbamoyl-4-methyl-thien-2-yl]3,5-dimethoxycinnamic amide;	347
259	N-[3-carbamoyl-4-methyl-thien-2-yl]2,4-dimethoxycinnamic amide;	347
260	N-[3-carbamoyl-4-methyl-thien-2-yl]3-(3,4-dimethoxyphenyl)propionamide;	349
261	N-[3-carbamoyl-4-methyl-thien-2-yl]9-fluorenecarboxamide;	349
262	N-[3-carbamoyl-4-methyl-thien-2-yl]6-chloro(2H)-1-benzopyran-3-carboxamide;	349
263	N-[3-carbamoyl-4-methyl-thien-2-yl]epsilon-maleimidocaproic amide;	350

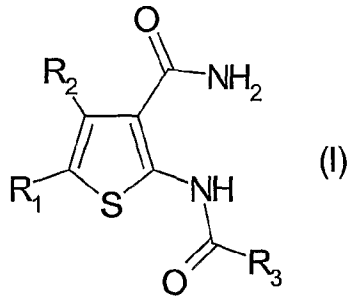
264	N-[3-carbamoyl-4-methyl-thien-2-yl]5-methoxyindole-2-carboxamide;	330
265	N-[3-carbamoyl-4-methyl-thien-2-yl]2,3,4-trimethoxybenzamide;	351
266	N-[3-carbamoyl-4-methyl-thien-2-yl]5-hydroxyindole-3-acetamide;	330
267	N-[3-carbamoyl-4-methyl-thien-2-yl]2,4,5-trimethoxybenzamide;	351
268	N-[3-carbamoyl-6-methyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl]3,4,5-trimethoxybenzamide;	406
269	N-[3-carbamoyl-6-methyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl]2,4,6-trimethoxybenzamide;	406
270	N-[3-carbamoyl-6-methyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl]3-chlorobenzo[b]thiophene-2-carboxamide;	406
271	N-[3-carbamoyl-6-methyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl]3-(phenylsulfonyl)propionamide;	408
272	N-[3-carbamoyl-6-methyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl]4-toluenesulfonylacetamide;	408
273	N-[3-carbamoyl-6-methyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl]4-methylsulfonylphenylacetamide;	408
274	N-[3-carbamoyl-6-methyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl]5-fluoroindole-3-acetamide;	387
275	N-[3-carbamoyl-6-methyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl]3-phthalimido-propionamide;	413
276	N-[3-carbamoyl-6-methyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl]5-methoxy-2-methyl-3-indoleacetamide;	417
277	N-[3-carbamoyl-6-methyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl]5-methoxy-1-indanone-3-acetamide;	414
278	N-[3-carbamoyl-6-methyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl]5-(4-chlorophenyl)-2-furoic amide;	416
279	N-[3-carbamoyl-6-methyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl]6-chlorokynurenic amide;	417
280	N-[3-carbamoyl-6-methyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl]N'-(4-chlorophenyl)maleamic amide;	419
281	N-[3-carbamoyl-6-methyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl]N'-p-tosylglycinamide;	423

282	N-[3-carbamoyl-6-methyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl]5-chloroindole-2-carboxamide;	389
283	N-[3-carbamoyl-6-methyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl]N'-(1-naphthyl)maleamic amide;	435
284	N-[3-carbamoyl-6-methyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl]3-iodobenzamide;	442
285	N-[3-carbamoyl-6-methyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl]4-iodobenzamide;	442
286	N-[3-carbamoyl-6-methyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl]N-m-tolylphthalamic amide;	449
287	N-[3-carbamoyl-6-methyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl]N'-acetyl-dl-histidine;	391
288	N-[3-carbamoyl-6-methyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl]3-acetamino-6-bromobenzamide;	452
289	N-[3-carbamoyl-6-methyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl]2-acetamido-5-bromobenzamide;	452
290	N-[3-carbamoyl-6-methyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl]2-iodophenylacetamide;	456
291	N-[3-carbamoyl-6-methyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl]4-iodophenylacetamide;	456
292	N-[3-carbamoyl-6-methyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl]8-(3-carboxamidopropyl)-1,3-dimethylxanthine;	460
293	N-[3-carbamoyl-6-methyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl]7-bromokynurenic amide;	462
294	N-[3-carbamoyl-6-methyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl]N'-benzoyl-dl-phenylalaninamide.	463
295	N-[3-carbamoyl-6-methyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl]indole-3-butyramide;	397
296	N-[3-carbamoyl-6-methyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl]4-chloroindole-3-acetamide;	403

297	N-[3-carbamoyl-6-methyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl]dl-desthiobiotin;	408
298	N-[3-carbamoyl-6-methyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl]4,6-dichloroindole-2-carboxamide;	424
299	N-[3-carbamoyl-6-methyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl]N'-benzoyl-histidinamide	453

CLAIMS

1. A method for treating diseases caused by and/or associated with an altered protein kinase activity which comprises administering to a mammal in need thereof an effective amount of a 3-aminocarbonyl-2-carboxamido-thiophene derivative represented by formula (I):



(I)

wherein

R_1 and R_2 are, independently from each other, hydrogen, halogen or an optionally substituted group selected from aryl, straight or branched C_1-C_6 alkyl or aryl C_1-C_6 alkyl; or, taken together with the thiophene bond to which they are linked, R_1 and R_2 form a $-(CH_2)_m-(NR_4)_n-(CH_2)_p-$ group wherein m and p are, each independently, an integer form 1 to 3, n is 0 or 1 and m+n+p is an integer from 3 to 5; and R_4 is hydrogen or an optionally substituted straight or branched C_1-C_6 alkyl group;

R_3 is a group, optionally further substituted, selected from:

i) straight or branched C_1-C_8 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl or C_2-C_6 alkylcarbonyl;

ii) aryl;

iii) 3 to 7 membered carbocycle;

iv) 5 to 7 membered heterocycle with from 1 to 3 heteroatoms selected from nitrogen, oxygen and sulfur;

or a pharmaceutically acceptable salt thereof.

2. The method of claim 1 wherein the disease caused by and/or associated with an altered protein kinase activity is a cell proliferative disorder selected from the group consisting of cancer, Alzheimer's disease, viral infections, auto-immune diseases and neurodegenerative disorders.

3. The method of claim 2 wherein the cancer is selected from carcinoma, squamous cell carcinoma, hematopoietic tumors of lymphoid or myeloid lineage, tumors of mesenchymal origin, tumors of the central and peripheral nervous system, melanoma, seminoma, teratocarcinoma, osteosarcoma, xeroderma pigmentosum, keratoacanthoma, thyroid follicular cancer and Kaposi's sarcoma.

4. The method of claim 1 wherein the cell proliferative disorder is selected from benign prostate hyperplasia, familial adenomatosis, polyposis, neuro-fibromatosis, psoriasis, vascular smooth cell proliferation associated with atherosclerosis, pulmonary fibrosis, arthritis glomerulonephritis and post-surgical stenosis and restenosis.

5. The method of claim 1 which provides tumor angiogenesis and metastasis inhibition.

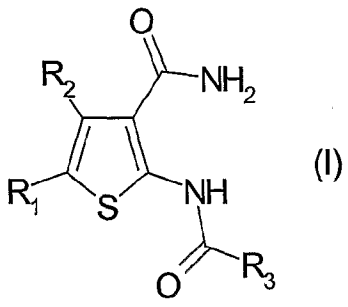
6. The method of claim 1 further comprising subjecting the mammal in need thereof to a radiation therapy or chemotherapy regimen in combination with at least one cytostatic or cytotoxic agent.

7. The method of claim 1 wherein the mammal in need thereof is a human.

8. The method of claim 1 wherein R_1 and R_2 are selected, each independently, from hydrogen, C_1-C_4 alkyl or optionally substituted aryl or aryl C_1-C_4 alkyl groups and R_3 is as defined in claim 1.

9. The method of claim 1 wherein R_1 and R_2, together, form a $-(CH_2)_m-(NR_4)_n-(CH_2)_p-$ group, n is 0 or 1, R_4 if present is C_1-C_4 alkyl, m, p and R_3 are as defined in claim 1.

10. A 3-aminocarbonyl-2-carboxamido-thiophene derivative represented by formula (I):



(I)

wherein

R_1 and R_2 are, independently from each other, hydrogen, halogen or an optionally substituted group selected from aryl, straight or branched C_1-C_6 alkyl or aryl C_1-C_6 alkyl; or, taken together with the thiophene bond to which they are linked, R_1 and R_2 form a $-(CH_2)_m-(NR_4)_n-(CH_2)_p-$ group wherein m and p are, each independently, an integer form 1 to 3, n is 0 or 1 and m+n+p is an integer from 3 to 5; and R_4 is hydrogen or an optionally substituted straight or branched C_1-C_6 alkyl group;

R_3 is a group, optionally further substituted, selected from:

i) straight or branched C_1-C_8 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl or C_2-C_6 alkylcarbonyl;

ii) aryl;

iii) 3 to 7 membered carbocycle;

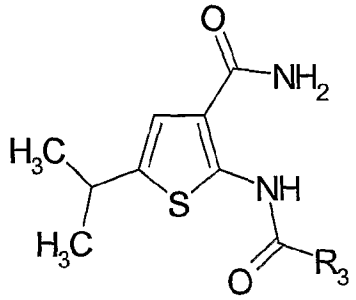
iv) 5 to 7 membered heterocycle with from 1 to 3 heteroatoms selected from nitrogen, oxygen and sulfur;

or a pharmaceutically acceptable salt thereof.

11. The compound of claim 10 wherein R_1 and R_2 are selected, each independently, from hydrogen, C_1-C_4 alkyl or optionally substituted aryl or aryl C_1-C_4 alkyl groups and R_3 is as defined in claim 10.

12. The compound of claim 10 wherein R_1 and R_2, together, form a $-(CH_2)_m-(NR_4)_n-(CH_2)_p-$ group, n is 0 or 1, R_4 if present is C_1-C_4 alkyl, m, p and R_3 are as defined in claim 10.

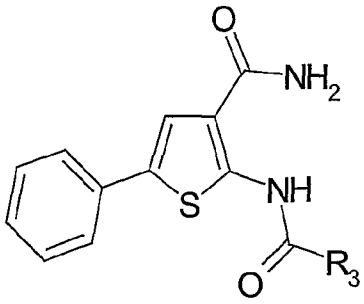
13. A 3-aminocarbonyl-2-carboxamido-thiophene derivative represented by formula (Ia)



(Ia)

wherein R_3 is as defined in claim 10.

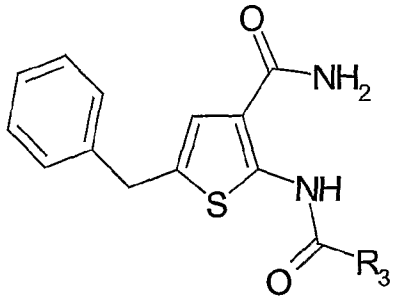
14. A 3-aminocarbonyl-2-carboxamido-thiophene derivative represented by formula (Ib)



(Ib)

wherein R_3 is as defined in claim 10; provided that R_3 is other than methyl, phenyl, 2-carboxyethyl, 2-thienyl, 2-furyl, pyrrolidin-1-yl-methyl or piperidyl-1-yl-methyl.

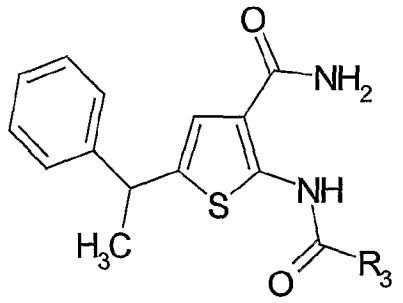
15. A 3-aminocarbonyl-2-carboxamido-thiophene derivative represented by formula (Ic)



(Ic)

wherein R_3 is as defined in claim 10.

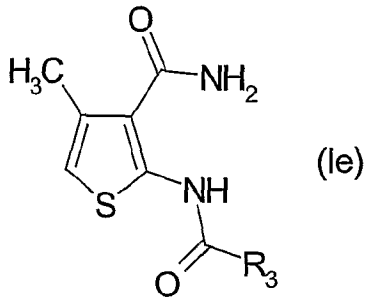
16. A 3-aminocarbonyl-2-carboxamido-thiophene derivative represented by formula (Id)



(Id)

wherein R_3 is as defined in claim 10.

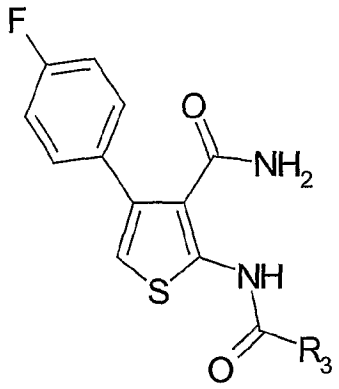
17. A 3-aminocarbonyl-2-carboxamido-thiophene derivative represented by formula (Ie)



(Ie)

wherein R_3 is as defined in claim 10; provided that R_3 is other than n-propyl, n-butyl or optionally further substituted nitrophenyl.

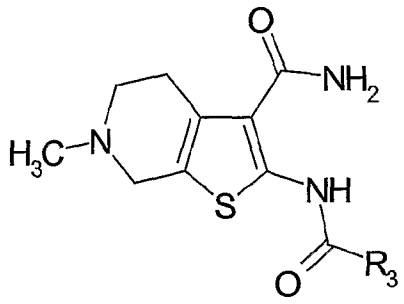
18. A 3-aminocarbonyl-2-carboxamido-thiophene derivative represented by formula (If)



(If)

wherein R_3 is as defined in claim 10.

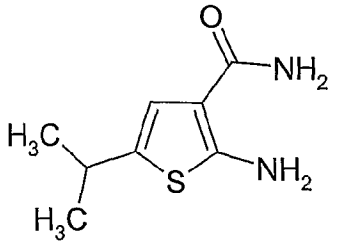
19. A 3-aminocarbonyl-2-carboxamido-thiophene derivative represented by formula (Ig)



(Ig)

wherein R_3 is as defined in claim 10; provided that R_3 is other than ethoxycarbonyl, ethoxycarbonylmethyl or methylcarbonylmethyl.

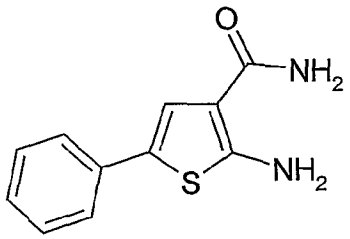
20. Any specific 3-aminocarbonyl-2-carboxamido-thiophene which is obtainable through a process comprising reacting the 2-amino-thiophene derivative of formula (II) below



(II)

with each one of the carboxylic acids listed in table II.

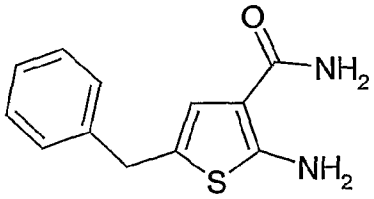
21. Any specific 3-aminocarbonyl-2-carboxamido-thiophene which is obtainable through a process comprising reacting the 2-amino-thiophene derivative of formula (II) below



(II)

with each one of the carboxylic acids listed in table II other than acetic, benzoic or thiophene-2-carboxylic acid.

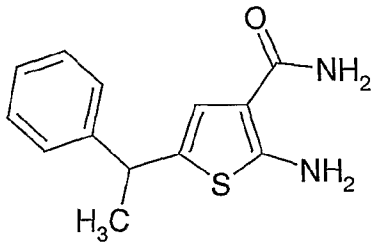
22. Any specific 3-aminocarbonyl-2-carboxamido-thiophene which is obtainable through a process comprising reacting the 2-amino-thiophene derivative of formula (II) below



(II)

with each one of the carboxylic acids of table II.

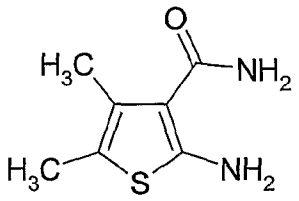
23. Any specific 3-aminocarbonyl-2-carboxamido-thiophene which is obtainable through a process comprising reacting the 2-amino-thiophene derivative of formula (II) below



(II)

with each one of the carboxylic acids of table II.

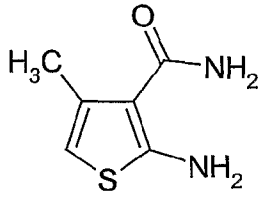
24. Any specific 3-aminocarbonyl-2-carboxamido-thiophene which is obtainable through a process comprising reacting the 2-amino-thiophene derivative of formula (II) below



(II)

with each one of the carboxylic acids of table II.

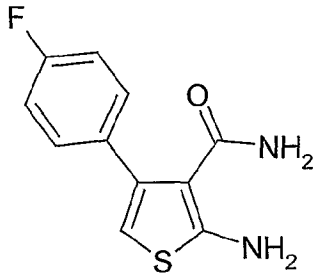
25. Any specific 3-aminocarbonyl-2-carboxamido-thiophene which is obtainable through a process comprising reacting the 2-amino-thiophene derivative of formula (II) below



(II)

with each one of the carboxylic acids of table II.

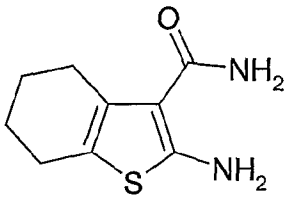
26. Any specific 3-aminocarbonyl-2-carboxamido-thiophene which is obtainable through a process comprising reacting the 2-amino-thiophene derivative of formula (II) below



(II)

with each one of the carboxylic acids of table II.

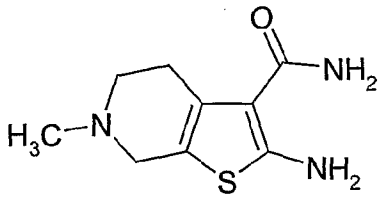
27. Any specific 3-aminocarbonyl-2-carboxamido-thiophene which is obtainable through a process comprising reacting the 2-amino-thiophene derivative of formula (II) below



(II)

with each one of the carboxylic acids of table II.

28. Any specific 3-aminocarbonyl-2-carboxamido-thiophene which is obtainable through a process comprising reacting the 2-amino-thiophene derivative of formula (II) below



(II)

with each one of the carboxylic acids of table II.

29. The compound of formula (I) according to claim 10, optionally in the form of a pharmaceutically acceptable salt, selected from the group consisting of:

1) N-[3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thien-2-yl]phenylacetamide;
2) N-[3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thien-2-yl]acetamide;

3) N-[3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thien-2-yl]propionamide;

4) N-[3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thien-2-yl]2-butynoic amide;

5) N-[3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thien-2-yl]cyanoacetamide;

6) N-[3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thien-2-yl]cyclopropanecarboxamide;

7) N-[3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thien-2-yl]isobutyramide;

8) N-[3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thien-2-yl]3,3-dimethylacrylic amide;

9) N-[3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thien-2-yl]2-ketobutyramide;

10) N-[3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thien-2-yl]N,N-dimethylglycinamide;

11) N-[3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thien-2-yl]3-chloropropionamide;

12) N-[3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thien-2-yl]imidazol-4-carboxamide;

13) N-[3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thien-2-yl]pyrrole-2-carboxamide;

14) N-[3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thien-2-yl]cyclopentanecarboxamide;

15) N-[3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thien-2-yl]1-cyanocyclopropanecarboxamide;

16) N-[3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thien-2-yl]N-acetylglycinamide;

17) N-[3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thien-2-yl]pyrrole-3-carboxamide;

18) N-[3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thien-2-yl]benzamide;

19) N-[3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thien-2-yl]4-pyrazolecarboxamide;

20) N-[3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thien-2-yl]picolinic amide;

21) N-[3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thien-2-yl]nicotinic amide;

22) N-[3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thien-2-yl]isonicotinic amide;

23) N-[3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thien-2-yl]2-pyrazinecarboxamide;

24) N-[3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thien-2-yl]1-methylpyrrole-2-carboxamide;

25) N-[3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thien-2-yl]3-methyl-2-furoic amide;

26) N-[3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thien-2-yl]5-methylisoxazole-4-carboxamide;

27) N-[3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thien-2-yl]3-methylisoxazole-4-carboxamide;

28) N-[3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thien-2-yl]thiophene-2-carboxamide;

29) N-[3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thien-2-yl]thiophene-3-carboxamide;

30) N-[3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thien-2-yl]dl-pyroglutamic amide;

31) N-[3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thien-2-yl]1-(aminocarbonyl)-1-cyclopropanecarboxamide;

32) N-[3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thien-2-yl]o-toluic amide;

33) N-[3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thien-2-yl]5-methylisoxazole-3-carboxamide;

34) N-[3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thien-2-yl]m-toluic amide;

35) N-[3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thien-2-yl]3-aminopyrazole-4-carboxamide;

36) N-[3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thien-2-yl]p-toluic amide;

37) N-[3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thien-2-yl]salicylic amide;

38) N-[3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thien-2-yl]3-hydroxybenzamide;

39) N-[3-carbamoyl-5-isopropyl-thien-2-yl]cyclopentylacetamide;

40) N-[3-carbamoyl-5-isopropyl-thien-2-yl]4-hydroxybenzamide;

41) N-[3-carbamoyl-5-isopropyl-thien-2-yl]5-norbornene-2-carboxamide;

42) N-[3-carbamoyl-5-isopropyl-thien-2-yl]2-fluorobenzamide;

43) N-[3-carbamoyl-5-isopropyl-thien-2-yl]2-imidazolidone-4-carboxamide;

44) N-[3-carbamoyl-5-isopropyl-thien-2-yl]3-fluorobenzamide;

45) N-[3-carbamoyl-5-isopropyl-thien-2-yl]N'-acetyl-dl-alaninamide;

46) N-[3-carbamoyl-5-isopropyl-thien-2-yl]4-fluorobenzamide;

47) N-[3-carbamoyl-5-isopropyl-thien-2-yl]3-ureidopropionamide;

48) N-[3-carbamoyl-5-isopropyl-thien-2-yl]thiophene-2-acetamide;

49) N-[3-carbamoyl-5-isopropyl-thien-2-yl]thiophene-3-acetamide;

50) N-[3-carbamoyl-5-isopropyl-thien-2-yl]3-cyclopentylpropionamide;

51) N-[3-carbamoyl-5-isopropyl-thien-2-yl]cycloheptanecarboxamide;

52) N-[3-carbamoyl-5-isopropyl-thien-2-yl]2,2-dimethylhexanoic amide;

53) N-[3-carbamoyl-5-isopropyl-thien-2-yl]alpha-(isopropylideneaminooxy)propionamide;

54) N-[3-carbamoyl-5-isopropyl-thien-2-yl]N,N-dimethylsuccinamic amide;

55) N-[3-carbamoyl-5-isopropyl-thien-2-yl]urocanic amide;

56) N-[3-carbamoyl-5-isopropyl-thien-2-yl]phenylpropiolic amide;

57) N-[3-carbamoyl-5-isopropyl-thien-2-yl]2-methylpyrazine-5-carboxamide;

58) N-[3-carbamoyl-5-isopropyl-thien-2-yl]3-cyanobenzamide;

59) N-[3-carbamoyl-5-isopropyl-thien-2-yl]4-cyanobenzamide;

60) N-[3-carbamoyl-5-isopropyl-thien-2-yl]N-methyl-l-proline monohydrate;

61) N-[3-carbamoyl-5-isopropyl-thien-2-yl]cinnamic amide;

62) N-[3-carbamoyl-5-isopropyl-thien-2-yl]3-(3-pyridyl)acrylic amide;

63) N-[3-carbamoyl-5-isopropyl-thien-2-yl]3,5-dimethylisoxazole-4-carboxamide;

64) N-[3-carbamoyl-5-isopropyl-thien-2-yl]3-(4-pyridyl)-acrylic amide;

65) N-[3-carbamoyl-5-isopropyl-thien-2-yl]2,3-dimethylbenzamide;

66) N-[3-carbamoyl-5-isopropyl-thien-2-yl]2,4-dimethylbenzamide;

67) N-[3-carbamoyl-5-isopropyl-thien-2-yl]2,5-dimethylbenzamide;

68) N-[3-carbamoyl-5-isopropyl-thien-2-yl]2,6-dimethylbenzamide;

69) N-[3-carbamoyl-5-isopropyl-thien-2-yl]3,4-dimethylbenzamide;

70) N-[3-carbamoyl-5-isopropyl-thien-2-yl]3,5-dimethylbenzamide;

71) N-[3-carbamoyl-5-isopropyl-thien-2-yl]2-phenylpropionamide;

72) N-[3-carbamoyl-5-isopropyl-thien-2-yl]3-phenylpropionamide;
73) N-[3-carbamoyl-5-isopropyl-thien-2-yl]N-carbamyl-dl-alpha-amino-n-butyramide;
74) N-[3-carbamoyl-5-isopropyl-thien-2-yl]o-tolylacetamide;
75) N-[3-carbamoyl-5-isopropyl-thien-2-yl]m-tolylacetamide;
76) N-[3-carbamoyl-5-isopropyl-thien-2-yl]p-tolylacetamide;
77) N-[3-carbamoyl-5-isopropyl-thien-2-yl]3-pyridinepropionamide;
78) N-[3-carbamoyl-5-phenyl-thien-2-yl]o-anisic amide;
79) N-[3-carbamoyl-5-phenyl-thien-2-yl]3-methylsalicylic amide;
80) N-[3-carbamoyl-5-phenyl-thien-2-yl]4-methylsalicylic amide;
81) N-[3-carbamoyl-5-phenyl-thien-2-yl]5-methylsalicylic amide;
82) N-[3-carbamoyl-5-phenyl-thien-2-yl]3-methoxybenzamide;
83) N-[3-carbamoyl-5-phenyl-thien-2-yl]3-hydroxy-4-methylbenzamide;
84) N-[3-carbamoyl-5-phenyl-thien-2-yl]p-anisic amide;
85) N-[3-carbamoyl-5-phenyl-thien-2-yl]phenoxyacetamide;
86) N-[3-carbamoyl-5-phenyl-thien-2-yl]2-hydroxyphenylacetamide;
87) N-[3-carbamoyl-5-phenyl-thien-2-yl]3-hydroxyphenylacetamide;
88) N-[3-carbamoyl-5-phenyl-thien-2-yl]4-hydroxyphenylacetamide;
89) N-[3-carbamoyl-5-phenyl-thien-2-yl]dl-mandelic amide;
90) N-[3-carbamoyl-5-phenyl-thien-2-yl]3-hydroxy-o-toluic amide;
91) N-[3-carbamoyl-5-phenyl-thien-2-yl]alpha-fluorophenylacetamide;

92) N-[3-carbamoyl-5-phenyl-thien-2-yl]2-fluorophenylacetamide;

93) N-[3-carbamoyl-5-phenyl-thien-2-yl]3-fluorophenylacetamide;

94) N-[3-carbamoyl-5-phenyl-thien-2-yl]4-fluorophenylacetamide;

95) N-[3-carbamoyl-5-phenyl-thien-2-yl]3-(2-thienyl)acrylic amide;

96) N-[3-carbamoyl-5-phenyl-thien-2-yl]3-(3-thienyl)-acrylic amide;

97) N-[3-carbamoyl-5-phenyl-thien-2-yl]3-(2-thienyl)propanoic amide;

98) N-[3-carbamoyl-5-phenyl-thien-2-yl]2-chlorobenzamide;

99) N-[3-carbamoyl-5-phenyl-thien-2-yl]3-chlorobenzamide;

100) N-[3-carbamoyl-5-phenyl-thien-2-yl]4-chlorobenzamide;

101) N-[3-carbamoyl-5-phenyl-thien-2-yl]N-propylmaleamic amide;

102) N-[3-carbamoyl-5-phenyl-thien-2-yl]N'-acetyl-dl-allylglycinamide;

103) N-[3-carbamoyl-5-phenyl-thien-2-yl]N'-acetyl-dl-prolinamide;

104) N-[3-carbamoyl-5-phenyl-thien-2-yl]3-(1-piperidine)propionamide;

105) N-[3-carbamoyl-5-phenyl-thien-2-yl]2-chloronicotinic amide;

106) N-[3-carbamoyl-5-phenyl-thien-2-yl]6-chloronicotinic amide;

107) N-[3-carbamoyl-5-phenyl-thien-2-yl]N-(acetoacetyl)glycinamide;

108) N-[3-carbamoyl-5-phenyl-thien-2-yl]N'-acetyl-dl-valinamide;

109) N-[3-carbamoyl-5-phenyl-thien-2-yl]dl-alanyl-dl-alanine;

110) N-[3-carbamoyl-5-phenyl-thien-2-yl]indole-6-carboxamide;

111) N-[3-carbamoyl-5-phenyl-thien-2-yl]benzofuran-2-carboxamide;

112) N-[3-carbamoyl-5-phenyl-thien-2-yl]1-phenyl-1-cyclopropanecarboxamide;

113) N-[3-carbamoyl-5-phenyl-thien-2-yl]cycloheptylacetamide;

114) N-[3-carbamoyl-5-phenyl-thien-2-yl]alpha-methylcinnamic amide;

115) N-[3-carbamoyl-5-phenyl-thien-2-yl]2-acetylbenzamide;

116) N-[3-carbamoyl-5-benzyl-thien-2-yl]4-acetylbenzamide;

117) N-[3-carbamoyl-5-benzyl-thien-2-yl]o-coumaric amide;

118) N-[3-carbamoyl-5-benzyl-thien-2-yl]3-hydroxycinnamic amide;

119) N-[3-carbamoyl-5-benzyl-thien-2-yl]4-hydroxycinnamic amide;

120) N-[3-carbamoyl-5-benzyl-thien-2-yl]p-coumaric amide;

121) N-[3-carbamoyl-5-benzyl-thien-2-yl]4-isopropylbenzamide;

122) N-[3-carbamoyl-5-benzyl-thien-2-yl]2-(3,5-xylyl)acetamide;

123) N-[3-carbamoyl-5-benzyl-thien-2-yl]phthalamic amide;

124) N-[3-carbamoyl-5-benzyl-thien-2-yl]N-carbamoylmaleamic amide;

125) N-[3-carbamoyl-5-benzyl-thien-2-yl]3-dimethylaminobenzamide;

126) N-[3-carbamoyl-5-benzyl-thien-2-yl]4-dimethylaminobenzamide;

127) N-[3-carbamoyl-5-benzyl-thien-2-yl]2-dimethylaminobenzamide;

128) N-[3-carbamoyl-5-benzyl-thien-2-yl]N'-carbamyl-dl-norvalinamide;

129) N-[3-carbamoyl-5-benzyl-thien-2-yl]piperonylic amide;

130) N-[3-carbamoyl-5-benzyl-thien-2-yl]N-carbamyl-dl-valine;

131) N-[3-carbamoyl-5-benzyl-thien-2-yl]alpha-fluorocinnamic amide;

132) N-[3-carbamoyl-5-benzyl-thien-2-yl]3-methoxy-4-methylbenzamide;

133) N-[3-carbamoyl-5-benzyl-thien-2-yl]indole-2-carboxamide;

134) N-[3-carbamoyl-5-benzyl-thien-2-yl]4-hydroxy-3,5-dimethylbenzamide;

135) N-[3-carbamoyl-5-benzyl-thien-2-yl]indole-3-carboxamide;

136) N-[3-carbamoyl-5-benzyl-thien-2-yl]benzyloxyacetamide;

137) N-[3-carbamoyl-5-benzyl-thien-2-yl]indole-5-carboxamide;

138) N-[3-carbamoyl-5-benzyl-thien-2-yl]4-dimethylaminobutyramide;

139) N-[3-carbamoyl-5-benzyl-thien-2-yl]indole-4-carboxamide;

140) N-[3-carbamoyl-5-benzyl-thien-2-yl]3-methoxysalicylic amide;

141) N-[3-carbamoyl-5-benzyl-thien-2-yl]4-methoxysalicylic amide;

142) N-[3-carbamoyl-5-benzyl-thien-2-yl]5-methoxysalicylic amide;

143) N-[3-carbamoyl-5-benzyl-thien-2-yl]5-benzimidazolecarboxamide;

144) N-[3-carbamoyl-5-benzyl-thien-2-yl]3-hydroxy-4-methoxybenzamide;

145) N-[3-carbamoyl-5-benzyl-thien-2-yl]indazole-3-carboxamide;

146) N-[3-carbamoyl-5-benzyl-thien-2-yl]vanillic amide;

147) N-[3-carbamoyl-5-benzyl-thien-2-yl]4-hydroxyphenoxyacetamide;

148) N-[3-carbamoyl-5-benzyl-thien-2-yl]6-methoxysalicylic amide;

149) N-[3-carbamoyl-5-benzyl-thien-2-yl]4-imidazoleacetamide;

150) N-[3-carbamoyl-5-benzyl-thien-2-yl]N-(2-furoyl)glycinamide;

151) N-[3-carbamoyl-5-benzyl-thien-2-yl]6-carboxypurine;

152) N-[3-carbamoyl-5-benzyl-thien-2-yl]beta-maleimidopropionamide;

153) N-[3-carbamoyl-5-benzyl-thien-2-yl]3,4-dihydro-2,2-dimethyl-4-oxo-2h-pyran-6-carboxamide;

154) N-[3-carbamoyl-5-(1-phenylethyl)-thien-2-yl]1-acetylpiperidine-4-carboxamide;

155) N-[3-carbamoyl-5-(1-phenylethyl)-thien-2-yl]1-naphthoic amide;

156) N-[3-carbamoyl-5-(1-phenylethyl)-thien-2-yl]2-naphthoic amide;

157) N-[3-carbamoyl-5-(1-phenylethyl)-thien-2-yl]4-chlorosalicylic amide;

158) N-[3-carbamoyl-5-(1-phenylethyl)-thien-2-yl]5-chlorosalicylic amide;

159) N-[3-carbamoyl-5-(1-phenylethyl)-thien-2-yl]3-chloro-4-hydroxybenzamide;

160) N-[3-carbamoyl-5-(1-phenylethyl)-thien-2-yl]3-chlorosalicylic amide;

161) N-[3-carbamoyl-5-(1-phenylethyl)-thien-2-yl]N'-acetyl-hydroxyproline;

162) N-[3-carbamoyl-5-(1-phenylethyl)-thien-2-yl]quinaldic amide;

163) N-[3-carbamoyl-5-(1-phenylethyl)-thien-2-yl]quinoline-3-carboxamide;

164) N-[3-carbamoyl-5-(1-phenylethyl)-thien-2-yl]quinoline-4-carboxamide;

165) N-[3-carbamoyl-5-(1-phenylethyl)-thien-2-yl]1-isoquinolinecarboxamide;

166) N-[3-carbamoyl-5-(1-phenylethyl)-thien-2-yl]quinoline-6-carboxamide;

167) N-[3-carbamoyl-5-(1-phenylethyl)-thien-2-yl]quinoline-8-carboxamide;

168) N-[3-carbamoyl-5-(1-phenylethyl)-thien-2-yl]6-acetamidohexanoic amide;

169) N-[3-carbamoyl-5-(1-phenylethyl)-thien-2-yl]N'-acetyl-dl-leucinamide;

170) N-[3-carbamoyl-5-(1-phenylethyl)-thien-2-yl]N',N'-di-n-propyl-l-alaninamide;

171) N-[3-carbamoyl-5-(1-phenylethyl)-thien-2-yl]N'-alpha-acetyl-l-asparaginamide;

172) N-[3-carbamoyl-5-(1-phenylethyl)-thien-2-yl]cinnoline-4-carboxamide;

173) N-[3-carbamoyl-5-(1-phenylethyl)-thien-2-yl]2-quinoxalinecarboxamide;

174) N-[3-carbamoyl-5-(1-phenylethyl)-thien-2-yl]3-methylindene-2-carboxamide;

175) N-[3-carbamoyl-5-(1-phenylethyl)-thien-2-yl]1-methylindole-2-carboxamide;

176) N-[3-carbamoyl-5-(1-phenylethyl)-thien-2-yl]1-methylindole-3-carboxamide;

177) N-[3-carbamoyl-5-(1-phenylethyl)-thien-2-yl]indazolone-4-carboxamide;

178) N-[3-carbamoyl-5-(1-phenylethyl)-thien-2-yl]3-oxo-1-indancarboxamide;

179) N-[3-carbamoyl-5-(1-phenylethyl)-thien-2-yl]1,2,3,4-tetrahydro-2-naphthoic amide;

180) N-[3-carbamoyl-5-(1-phenylethyl)-thien-2-yl]2-indanylacetamide;

181) N-[3-carbamoyl-5-(1-phenylethyl)-thien-2-yl]1-methyl-4-imidazole-acetamide;

182) N-[3-carbamoyl-5-(1-phenylethyl)-thien-2-yl]arecaidinamide;

183) N-[3-carbamoyl-5-(1-phenylethyl)-thien-2-yl]3-benzoylpropionamide;

184) N-[3-carbamoyl-5-(1-phenylethyl)-thien-2-yl]4-methoxycinnamic amide;

185) N-[3-carbamoyl-5-(1-phenylethyl)-thien-2-yl]2-methoxycinnamic amide;

186) N-[3-carbamoyl-5-(1-phenylethyl)-thien-2-yl]benzo[b]thiophene-2-carboxamide;

187) N-[3-carbamoyl-5-(1-phenylethyl)-thien-2-yl]2-isopropyl-2-phenylacetamide;

188) N-[3-carbamoyl-5-(1-phenylethyl)-thien-2-yl]N'-acetylanthranilic amide;

189) N-[3-carbamoyl-5-(1-phenylethyl)-thien-2-yl]4-acetamidobenzamide;

190) N-[3-carbamoyl-5-(1-phenylethyl)-thien-2-yl]hippuric amide;

191) N-[3-carbamoyl-5-(1-phenylethyl)-thien-2-yl]3-acetamidobenzamide;

192) N-[3-carbamoyl-4,5-dimethyl-thien-2-yl]3,4-methylenedioxyphenylacetamide;

193) N-[3-carbamoyl-4,5-dimethyl-thien-2-yl]nicotinuric amide;

194) N-[3-carbamoyl-4,5-dimethyl-thien-2-yl]4-isopropoxybenzamide;

195) N-[3-carbamoyl-4,5-dimethyl-thien-2-yl]3-(diethylamino)propionamide;

196) N-[3-carbamoyl-4,5-dimethyl-thien-2-yl]2,5-dimethoxybenzamide;

197) N-[3-carbamoyl-4,5-dimethyl-thien-2-yl]2,6-dimethoxybenzamide;

198) N-[3-carbamoyl-4,5-dimethyl-thien-2-yl]3,4-dimethoxybenzamide;

199) N-[3-carbamoyl-4,5-dimethyl-thien-2-yl]3,5-dimethoxybenzamide;

200) N-[3-carbamoyl-4,5-dimethyl-thien-2-yl]2-methoxyphenoxyacetamide;

201) N-[3-carbamoyl-4,5-dimethyl-thien-2-yl]1-thymineacetamide;

202) N-[3-carbamoyl-4,5-dimethyl-thien-2-yl]indole-3-acetamide;

203) N-[3-carbamoyl-4,5-dimethyl-thien-2-yl]3-(2-thenoyl)-propionamide;

204) N-[3-carbamoyl-4,5-dimethyl-thien-2-yl]3-chloro-4-methoxybenzamide;

205) N-[3-carbamoyl-4,5-dimethyl-thien-2-yl]5-methylindole-2-carboxamide;

206) N-[3-carbamoyl-4,5-dimethyl-thien-2-yl]5-chloro-2-methoxybenzamide;

207) N-[3-carbamoyl-4,5-dimethyl-thien-2-yl]1-(2-carboxyphenyl)pyrrole;

208) N-[3-carbamoyl-4,5-dimethyl-thien-2-yl]4-(1-H-pyrrol-1-yl)benzamide;

209) N-[3-carbamoyl-4,5-dimethyl-thien-2-yl]1-methyl-3-indoleacetamide;

210) N-[3-carbamoyl-4,5-dimethyl-thien-2-yl]2-methyl-1h-benzimidazole-5-carboxamide;

211) N-[3-carbamoyl-4,5-dimethyl-thien-2-yl]2-(trifluoromethyl)benzamide;

212) N-[3-carbamoyl-4,5-dimethyl-thien-2-yl]3-(trifluoromethyl)benzamide;

213) N-[3-carbamoyl-4,5-dimethyl-thien-2-yl]4-(trifluoromethyl)benzamide;

214) N-[3-carbamoyl-4,5-dimethyl-thien-2-yl]chromone-2-carboxamide;

215) N-[3-carbamoyl-4,5-dimethyl-thien-2-yl]5-hydroxyindole-2-carboxamide;

216) N-[3-carbamoyl-4,5-dimethyl-thien-2-yl]chromone-3-carboxamide;

217) N-[3-carbamoyl-4,5-dimethyl-thien-2-yl]3-hydroxy-2-quinoxalinecarboxamide;

218) N-[3-carbamoyl-4,5-dimethyl-thien-2-yl]1-phenyl-1-cyclopentanecarboxamide;

219) N-[3-carbamoyl-4,5-dimethyl-thien-2-yl]2,3-dichlorobenzamide;

220) N-[3-carbamoyl-4,5-dimethyl-thien-2-yl]2,4-dichlorobenzamide;

221) N-[3-carbamoyl-4,5-dimethyl-thien-2-yl]2,5-dichlorobenzamide;

222) N-[3-carbamoyl-4,5-dimethyl-thien-2-yl]2,6-dichlorobenzamide;

223) N-[3-carbamoyl-4,5-dimethyl-thien-2-yl]3,4-dichlorobenzamide;

224) N-[3-carbamoyl-4,5-dimethyl-thien-2-yl]3,5-dichlorobenzamide;

225) N-[3-carbamoyl-4,5-dimethyl-thien-2-yl]4-oxophenylamino-2-butenoic amide;

226) N-[3-carbamoyl-4,5-dimethyl-thien-2-yl]4-(dimethylamino)cinnamic amide;

227) N-[3-carbamoyl-4,5-dimethyl-thien-2-yl]N'-chloroacetyl-dl-2-amino-n-butyramide;

228) N-[3-carbamoyl-4,5-dimethyl-thien-2-yl]3,4-methylenedioxycinnamic amide;

229) N-[3-carbamoyl-4,5-dimethyl-thien-2-yl]7-methoxybenzofuran-2-carboxamide;

230) N-[3-carbamoyl-4,5-dimethyl-thien-2-yl]4-benzoylbutyramide;

231) N-[3-carbamoyl-4-methyl-thien-2-yl]benzo[b]thiophene-3-acetamide;

232) N-[3-carbamoyl-4-methyl-thien-2-yl]N'-benzoyl-beta-alaninamide;

233) N-[3-carbamoyl-4-methyl-thien-2-yl]N'-acetyl-dl-phenylglycinamide;

234) N-[3-carbamoyl-4-methyl-thien-2-yl]N'-benzoyl-dl-alaninamide;

235) N-[3-carbamoyl-4-methyl-thien-2-yl]N'-methylhippuric amide;

236) N-[3-carbamoyl-4-methyl-thien-2-yl]o-hydroxyhippuric amide;

237) N-[3-carbamoyl-4-methyl-thien-2-yl]N'-(furan-2-yl-acryl)-glycinamide;

238) N-[3-carbamoyl-4-methyl-thien-2-yl](3,5-dimethoxyphenyl)acetamide;

239) N-[3-carbamoyl-4-methyl-thien-2-yl]3,5-dimethoxy-4-methylbenzamide;

240) N-[3-carbamoyl-4-methyl-thien-2-yl](2,4-dimethoxy-phenyl)-acetamide;

241) N-[3-carbamoyl-4-methyl-thien-2-yl]5-(2-thienoyl)butyramide;

242) N-[3-carbamoyl-4-methyl-thien-2-yl]4-(methylsulfonyl)benzamide;

243) N-[3-carbamoyl-4-methyl-thien-2-yl]phenylsulfonylacetamide;

244) N-[3-carbamoyl-4-methyl-thien-2-yl]3-indolepropionamide;

245) N-[3-carbamoyl-4-methyl-thien-2-yl]3-(methylsulfonyl)benzamide;

246) N-[3-carbamoyl-4-methyl-thien-2-yl]2-methyl-3-indoleacetamide;

247) N-[3-carbamoyl-4-methyl-thien-2-yl]2-(methylsulfonyl)benzamide;

248) N-[3-carbamoyl-4-methyl-thien-2-yl]4-sulfonamidobenzamide;

249) N-[3-carbamoyl-4-methyl-thien-2-yl]5-methyl-1-phenylpyrazole-4-carboxamide;

250) N-[3-carbamoyl-4-methyl-thien-2-yl]5-methyl-3-phenylisoxazole-4-carboxamide;

251) N-[3-carbamoyl-4-methyl-thien-2-yl]2-hydroxy-5-(1 h-pyrrol-1-yl)benzamide;

252) N-[3-carbamoyl-4-methyl-thien-2-yl]4-methyl-2-phenyl-1,2,3-triazole-5-carboxamide;

253) N-[3-carbamoyl-4-methyl-thien-2-yl]N'-acetyl-dl-phenylglycinamide;

254) N-[3-carbamoyl-4-methyl-thien-2-yl]2,3-dimethoxycinnamic amide;

255) N-[3-carbamoyl-4-methyl-thien-2-yl]2-benzimidazolepropionamide;

256) N-[3-carbamoyl-4-methyl-thien-2-yl]2,5-dimethoxycinnamic amide;

257) N-[3-carbamoyl-4-methyl-thien-2-yl]3,4-dimethoxycinnamic amide;

258) N-[3-carbamoyl-4-methyl-thien-2-yl]3,5-dimethoxycinnamic amide;

259) N-[3-carbamoyl-4-methyl-thien-2-yl]2,4-dimethoxycinnamic amide;

260) N-[3-carbamoyl-4-methyl-thien-2-yl]3-(3,4-dimethoxyphenyl)propionamide;

261) N-[3-carbamoyl-4-methyl-thien-2-yl]9-fluorenecarboxamide;

262) N-[3-carbamoyl-4-methyl-thien-2-yl]6-chloro(2H)-1-benzopyran-3-carboxamide;

263) N-[3-carbamoyl-4-methyl-thien-2-yl]epsilon-maleimidocaproic amide;

264) N-[3-carbamoyl-4-methyl-thien-2-yl]5-methoxyindole-2-carboxamide;

265) N-[3-carbamoyl-4-methyl-thien-2-yl]2,3,4-trimethoxybenzamide;

266) N-[3-carbamoyl-4-methyl-thien-2-yl]5-hydroxyindole-3-acetamide;

267) N-[3-carbamoyl-4-methyl-thien-2-yl]2,4,5-trimethoxybenzamide;

268) N-[3-carbamoyl-6-methyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl]3,4,5-trimethoxybenzamide;

269) N-[3-carbamoyl-6-methyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl]2,4,6-trimethoxybenzamide;

270) N-[3-carbamoyl-6-methyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl]3-chlorobenzo[b]thiophene-2-carboxamide;

271) N-[3-carbamoyl-6-methyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl]3-(phenylsulfonyl)propionamide;

272) N-[3-carbamoyl-6-methyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl]4-toluenesulfonylacetamide;

273) N-[3-carbamoyl-6-methyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl]4-methylsulfonylphenylacetamide;

274) N-[3-carbamoyl-6-methyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl]5-fluoroindole-3-acetamide;

275) N-[3-carbamoyl-6-methyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl]3-phthalimido-propionamide;

276) N-[3-carbamoyl-6-methyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl]5-methoxy-2-methyl-3-indoleacetamide;

277) N-[3-carbamoyl-6-methyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl]5-methoxy-1-indanone-3-acetamide;

278) N-[3-carbamoyl-6-methyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl]5-(4-chlorophenyl)-2-furoic amide;

279) N-[3-carbamoyl-6-methyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl]6-chlorokynurenic amide;

280) N-[3-carbamoyl-6-methyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl]N'-(4-chlorophenyl)maleamic amide;

281) N-[3-carbamoyl-6-methyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl]N'-p-tosylglycinamide;

282) N-[3-carbamoyl-6-methyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl]5-chloroindole-2-carboxamide;

283) N-[3-carbamoyl-6-methyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl]N'-(1-naphthyl)maleamic amide;

284) N-[3-carbamoyl-6-methyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl]3-iodobenzamide;

285) N-[3-carbamoyl-6-methyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl]4-iodobenzamide;

286) N-[3-carbamoyl-6-methyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl]N-m-tolylphthalamic amide;

287) N-[3-carbamoyl-6-methyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl]N'-acetyl-dl-histidine;

288) N-[3-carbamoyl-6-methyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl]3-acetamino-6-bromobenzamide;

289) N-[3-carbamoyl-6-methyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl]2-acetamido-5-bromobenzamide;

290) N-[3-carbamoyl-6-methyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl]2-iodophenylacetamide;

291) N-[3-carbamoyl-6-methyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl]4-iodophenylacetamide;

292) N-[3-carbamoyl-6-methyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl]8-(3-carboxamidopropyl)-1,3-dimethylxanthine;

293) N-[3-carbamoyl-6-methyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl]7-bromokynurenic amide;

294) N-[3-carbamoyl-6-methyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl]N'-benzoyl-dl-phenylalaninamide.

295) N-[3-carbamoyl-6-methyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl]indole-3-butyramide;

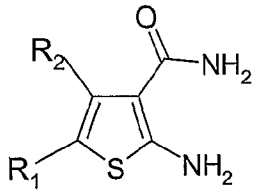
296) N-[3-carbamoyl-6-methyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl]4-chloroindole-3-acetamide;

297) N-[3-carbamoyl-6-methyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl]dl-desthiobiotin;

298) N-[3-carbamoyl-6-methyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl]4,6-dichloroindole-2-carboxamide;

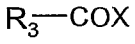
299) N-[3-carbamoyl-6-methyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl]N'-benzoyl-histidinamide.

30. A process for preparing the 3-aminocarbonyl-2-carboxamido-thiophene of claim 10, or a pharmaceutically acceptable salts thereof, which process comprises reacting a compound of formula (II)



(II)

wherein R_1 and R_2 are as defined in claim 10,
with a compound of formula (III)



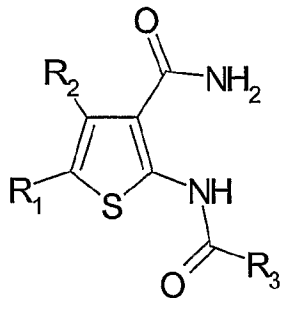
(III)

wherein R_3 is as defined in claim 10 and X is hydroxy or a suitable leaving group; and, if desired, converting a 2-aminocarbonyl-3-carboxamido-thiophene derivative of formula (I) into another such derivative of formula (I), and/or into a salt thereof.

31. The process of claim 30 wherein the X leaving group, within formula (III), is a halogen atom.

32. The process of claim 30 wherein X is hydroxy, chlorine or bromine.

33. A library of two or more compounds selected from 3-aminocarbonyl-2-carboxamido-thiophene derivatives of formula (I)



(I)

wherein
R_1 and R_2 are, independently from each other, hydrogen, halogen or an optionally substituted group selected from aryl, straight or branched C_1-C_6 alkyl or aryl C_1-C_6 alkyl; or, taken together with the thiophene bond to which they

are linked, R_1 and R_2 form a $-(CH_2)_m-(NR_4)_n-(CH_2)_p-$ group wherein m and p are, each independently, an integer form 1 to 3, n is 0 or 1 and m+n+p is an integer from 3 to 5; and R_4 is hydrogen or an optionally substituted straight or branched C_1-C_6 alkyl group;

R_3 is a group, optionally further substituted, selected from:

i) straight or branched C_1-C_8 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl or C_2-C_6 alkylcarbonyl;

ii) aryl;

iii) 3 to 7 membered carbocycle;

iv) 5 to 7 membered heterocycle with from 1 to 3 heteroatoms selected from nitrogen, oxygen and sulfur;

or a pharmaceutically acceptable salt thereof.

34. A pharmaceutical composition comprising an effective amount of a 3-aminocarbonyl-2-carboxamido-thiophene of formula (I) as defined in claim 10 and, at least, one pharmaceutically acceptable excipient, carrier or diluent.

35. A pharmaceutical composition according to claim 34 further comprising one or more chemotherapeutic agents, as a combined preparation for simultaneous, separate or sequential use in anticancer therapy.

36. A product or kit comprising a compound of claim 10 or a pharmaceutical composition thereof as defined in claim 34, and one or more chemotherapeutic agents, as a combined preparation for simultaneous, separate or sequential use in anticancer therapy.

37. A compound of formula (I) or a pharmaceutically acceptable salt thereof, as defined in claim 10, for use as a medicament.

38. Use of a compound of formula (I) or a pharmaceutically acceptable salt thereof, as defined in claim 10, in the manufacture of a medicament for treating diseases caused by and/or associated with an altered protein kinase activity.

39. Use according to claim 38 for treating tumors.

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(54) Title: THIOPHENE DERIVATIVES ACTIVE AS KINASE INHIBITORS, PROCESS FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS COMPRISING THEM

(57) Abstract: Compounds which are 3-aminocarbonyl-2-carboxamido-thiophene derivatives or pharmaceutically acceptable salts thereof, together with pharmaceutical compositions comprising them are disclosed; these compounds or compositions are useful in the treatment of diseases caused by and/or associated with an altered protein kinase activity such as cancer, cell proliferative disorders, Alzheimer's disease, viral infections, auto-immune diseases and neurodegenerative disorders.

I' ERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D333/38 C07D333/68 C07D417/04 C07D409/04 C07D515/04
A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
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Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Schmid, A

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